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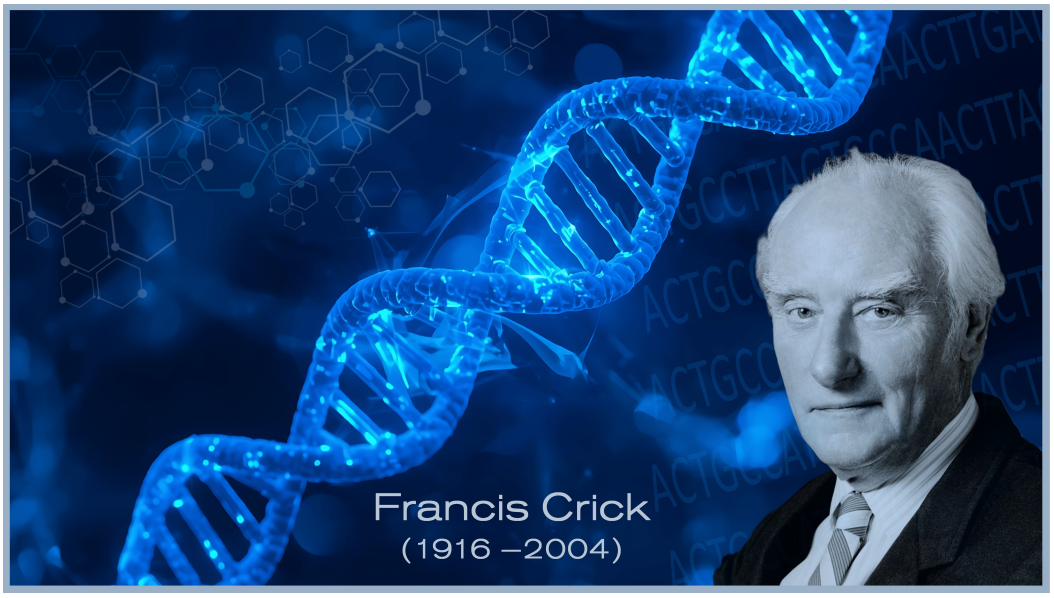

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Prvi broj *Vojnosanitetskog pregleda* izašao je septembra meseca 1944. godine
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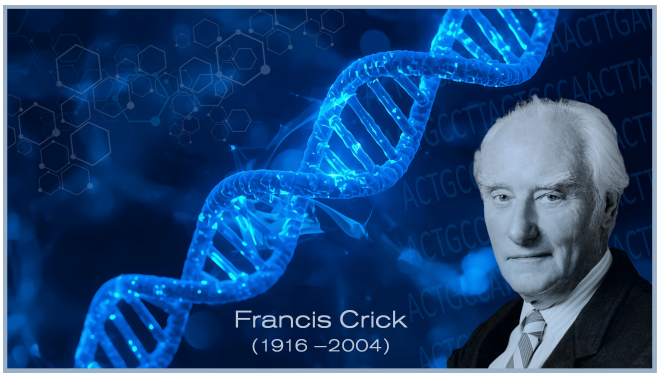

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This year, on June 8, marks the 110th anniversary of the birth of Francis Crick (1916–2004), one of the most influential scientists of the 20th century. In 1953, James Watson and Francis Crick published the discovery of the structure of deoxyribonucleic acid (DNA), a double helix formed by two polynucleotide chains, and the concept of genetic replication, in two scientific papers in the journal Nature. Together with Maurice Wilkins, Watson and Crick shared the 1962 Nobel Prize in Physiology or Medicine for their discoveries concerning the molecular structure of nucleic acids and its significance for information transfer in living material. This discovery provided crucial insights into the nature of the genetic code and the mechanisms of protein synthesis and represents one of the greatest milestones in the history of science.

Ove godine, 8. juna, obeležava se 110 godina od rođenja Frensisa Krika (1916–2004), jednog od najuticajnijih naučnika 20. veka. Otkriće strukture dezoksiribonukleinske kiseline (DNK), dvostruke spiralne zavojnice koju formiraju dva polinukleotidna lanca, i koncept genetske replikacije, Džejms Vatson i Frensis Krik su objavili 1953. u dva naučna rada u časopisu Nature. Zajedno sa Morisom Vilkinsom, Vatson i Krik dele Nobelovu nagradu za fiziologiju ili medicinu koju su dobili 1962. za njihova otkrića u vezi sa molekularnom strukturom nukleinskih kiselina i njenim značajem za prenos informacija u živim sistemima. Ovo otkriće je omogućilo ključne uvide u prirodu genetskog koda i mehanizme sinteze proteina i predstavlja jednu od prekretnica u istoriji nauke.

ORIGINAL ARTICLES

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Construction of an early prediction model for exacerbation of pneumonia caused by *Mycoplasma pneumoniae* in children: an incremental value study based on dynamic changes in C-reactive protein and IgG subclasses

Konstrukcija modela za rano predviđanje egzacerbacije pneumonije izazvane *Mycoplasmom pneumoniae* kod dece: studija inkrementalne vrednosti zasnovana na dinamičkim promenama C-reaktivnog proteina i potklasa IgG

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[1] the two authors contributed equally to this study

Abstract

Background/Aim. Exacerbation of *Mycoplasma pneumoniae* pneumonia (MPP) in children commonly manifests as severe or refractory disease. The aim of this study was to evaluate the predictive value of the dynamic percentage change in C-reactive protein – CRP (ΔCRP%) and immunoglobulin (Ig) G1 subclass for the exacerbation of MPP in children, and to determine whether their incorporation into the basic prediction model improves the prediction of disease exacerbation. **Methods.** This retrospective study included hospitalized pediatric patients diagnosed with MPP between 2020 and 2023, who were enrolled and stratified according to the occurrence of MPP exacerbation. Baseline clinical characteristics, laboratory parameters, serial CRP measurements (at 0 and 72 hrs), and IgG1–IgG4 subclass levels were collected. According to the predicted probabilities generated by the enhanced model, patients were categorized into three risk groups: low-risk (< 0.20), medium-risk (0.20–0.35), and high-risk (≥ 0.35). **Results.** Among the 512 pediatric patients, 110 (21.5%) experienced MPP exacerbation. Multivariate analysis identified fever duration, bilateral lung involvement, decreased lymphocyte percentage, elevated lactate dehydrogenase, increased D-dimer, higher ΔCRP% (*per* 10 percentage-point increase), and low IgG1 levels as independent predictors ($p < 0.05$). The enhanced model demonstrated superior discriminative performance, with an area under the receiver operating characteristic (ROC) curve (AUC) of 0.873, significantly higher than that of the basic model (0.792; $p = 0.004$). Risk stratification analysis showed a progressive increase in the observed exacerbation rate across the low-, medium-, and high-risk groups (approximately 10%, 30%, and 50%, respectively). **Conclusion.** Both ΔCRP% and low IgG1 levels are independent predictors of MPP exacerbation in children. The incorporation of these markers significantly improves the model's discrimination, calibration, and clinical utility for predicting the risk of disease progression.

Keywords:
biomarkers; c-reactive protein; disease progression; immunoglobulin g; models, statistical; mycoplasma pneumoniae; pneumonia, mycoplasma; prognosis.

Apstrakt

Uvod/Cilj. Egzacerbacija (pogoršanje) pneumonije izazvane *Mycoplasmom pneumoniae* (*Mycoplasma pneumoniae* pneumonija – MPP) kod dece obično se manifestuje kao teška ili refraktorna bolest. Cilj rada bio je da se proceni prediktivna vrednost dinamičke procentualne promene C-reaktivnog proteina – CRP (ΔCRP%) i potklase imunoglobulina (Ig) G1 za pogoršanje MPP kod dece kao i da se utvrdi da li njihovo uključivanje u osnovni prediktivni model poboljšava predviđanje pogoršanja bolesti. **Metode.** Ovom retrospektivnom studijom obuhvaćeni su pedijatrijski

Correspondence to: Huiqiong Liu, The Affiliated Cangnan Hospital of Wenzhou Medical University, The People's Hospital of Cangnan, Department of Pediatrics, Wenzhou 325 800, Zhejiang Province, China. E-mail: liuhqphc@wl-asia.com

bolesnici sa dijagnozom MPP u periodu između 2020. i 2023. godine, koji su uključeni u studiju i svrstani u grupe prema pojavi pogoršanja MPP. Prikupljeni su početni klinički podaci, laboratorijski parametri, rezultati serijskih merenja CRP-a (u 0. i 72. satu), kao i nivoi potklasa IgG1–IgG4. Prema predviđenim verovatnoćama koje je generisao unapređeni model, bolesnici su podeljeni u tri grupe rizika: nizak rizik (< 0,20), srednji rizik (0,20–0,35) i visok rizik (≥ 0,35). **Rezultati.** Od 512 pedijatrijskih bolesnika, kod njih 110 (21,5%) zabeleženo je pogoršanje MPP. Multivarijantnom analizom kao nezavisni prediktori identifikovani su trajanje groznice, obostrana zahvaćenost pluća, snižen procenat limfocita, povišena laktat dehidrogenaza, povišen D-dimer, viši ΔCRP% (po povećanju od 10 procentnih poena) i niski nivoi IgG1 ($p < 0,05$). Unapređeni model je pokazao bolju diskriminativnu sposobnost, sa vrednošću površine ispod *receiver operating characteristic* (ROC) krive (*area under the curve* – AUC) od 0,873, što je značajno više nego kod osnovnog modela (0,792; $p = 0,004$). Analizom stratifikacije rizika pokazano je progresivno povećanje stope primećenih egzacerbacija u grupama niskog, srednjeg i visokog rizika (približno 10%, 30% i 50%, redom). **Zaključak.** I ΔCRP% i niski nivoi IgG1 nezavisni su prediktori egzacerbacije MPP kod dece. Uključivanje tih markera značajno poboljšava diskriminativnu sposobnost, kalibraciju i kliničku korisnost modela za predviđanje rizika od progresije bolesti.

Ključne reči:
biomarkeri; c-reaktivni protein; bolest, progresija; imunoglobulin g; modeli, statistički; mycoplasma pneumoniae; pneumonija, mikoplazma; prognoza.

Introduction

Mycoplasma pneumoniae (MP) is one of the most common pathogens responsible for community-acquired pneumonia in children, accounting for approximately 10–40% of cases among hospitalized pediatric patients [1]. Although most children experience mild disease with favorable outcomes, the incidence rate of MP pneumonia (MPP) exacerbation has increased in recent years. For example, a 2024 study involving 526 pediatric patients with MPP reported that approximately 12% developed severe disease [2]. These severe cases are characterized by a higher incidence of lung consolidation, progressive lung injury, and even respiratory failure compared with non-severe cases, resulting in prolonged hospitalization, increased treatment complexity, and a greater burden on healthcare resources. Although the pathogenesis of MPP remains incompletely understood, accumulating evidence suggests that a dysregulated inflammatory response, an immune dysfunction, and pathogen virulence are key contributing factors [3].

Currently, early identification of MPP exacerbation remains a major challenge in clinical practice. Most existing studies focus on risk assessment based on single inflammatory markers, imaging findings, or routine clinical variables at admission [4]. However, these methods may not adequately capture disease progression, as they rely on static measurements and fail to reflect the dynamic nature of the inflammatory response. For instance, C-reactive protein (CRP) is a commonly used inflammatory biomarker, but its predictive value based on a single measurement is limited by substantial inter-individual variability [5]. Emerging evidence indicates that CRP is not only a marker of inflammation but may also contribute to lung epithelial cell injury by activating p38 mitogen-activated protein kinase and mitochondrial apoptotic pathways, thereby being associated with worse clinical outcomes [6]. Moreover, immune function plays a critical role in MPP progression [7]. A previous study has shown that children with MPP exacerbation exhibit impaired activation of T cells, an imbalance in $CD4^+/CD8^+$ T-cell subsets, and reduced anti-inflammatory capacity [8]. Despite these findings, the role of immunoglobulin (Ig) G subclasses, such as IgG1, in the exacerbation of MPP remains insufficiently explored. Moreover, the relationship between humoral immune reserve indicators (such as IgG subclasses) and the risk of disease exacerbation has not been systematically investigated.

Therefore, the aim of this study was to evaluate the predictive value of the dynamic percentage change in CRP (ΔCRP%) and IgG subclasses for MPP exacerbation in children, integrating both inflammatory dynamics and humoral immune status by using the basic model (BM) and enhanced model (EM). This integrated approach aims to provide a practical tool for early risk stratification and individualized management of MPP exacerbation in children.

Methods

Study design and sample size estimation

A single-center retrospective cohort design was adopted in this study. According to the events *per* variable principle for prediction modeling, at least 10 outcome events are required *per* variable independent principle. Based on a planned inclusion of 12–15 candidate predictors, a minimum of 120 severe events was required. Considering the previously reported incidence of MPP exacerbation in children (approximately 20–25%), the estimated total sample size ranged from 480 to 600 cases. All consecutive patients meeting the inclusion criteria during the study period were screened, and only those with complete data for key variables, including CRP measurements at both 0 and 72 hrs and IgG subclass levels, were included in the final analysis. No cases with missing data for these variables were retained, and a complete-case analysis was performed. A total of 512 pediatric patients were ultimately enrolled, including 110 (21.5%) cases of MPP exacerbation, thereby meeting the predefined sample size requirements and ensuring adequate statistical power.

Subjects and eligibility criteria

Children diagnosed with MPP and hospitalized between January 2020 and December 2023 were consecutively en-

rolled. Complete clinical data, laboratory results, IgG subclass measurements, and follow-up information were available for all included patients. The study was approved by the Ethics Committee of the People's Hospital of Cangnan, China (from January 02, 2020), and all procedures complied with relevant ethical standards.

Inclusion criteria were as follows: age 1 to 16 years; meeting at least one of the following clinical and etiological diagnostic criteria for MPP [9]: a positive MP polymerase chain reaction (PCR) result from throat swabs or respiratory secretions, an MP-specific IgM antibody titer ≥ 1 : 160 or a ≥ 4-fold increase in paired sera, and completion of CRP measurements at 0 and 72 hrs after admission.

The exclusion criteria were the following: diagnosed immunodeficiency or ongoing long-term immunosuppressive therapy; co-infection with other pathogens (such as influenza virus, adenovirus, or *Streptococcus* (*S.*) *pneumoniae*, etc.) or mixed infections, and presence of severe underlying diseases (such as congenital heart disease, neuromuscular disease, or chronic lung disease).

Etiological confirmation

Respiratory specimens were collected to detect MP deoxyribonucleic acid – DNA using real-time fluorescence quantitative PCR, which served as a primary basis for confirming the diagnosis of MPP. Commercial nucleic acid amplification kits (Daan Gene, Guangzhou, China) were used according to the manufacturer's instructions, with a cycle threshold value < 35 considered positive. To exclude mixed infections, all patients were concurrently screened for common respiratory viruses and bacterial pathogens, such as influenza virus, adenovirus, respiratory syncytial virus, and *S. pneumoniae*. Only patients with confirmed single MP infection were included in the subsequent modeling and analysis.

Collection of clinical data

Baseline data, including age, gender, previous illnesses, fever duration prior to admission, presence of wheezing, extent of radiological involvement (unilateral or bilateral), and use of glucocorticoid during hospitalization, were collected.

All imaging findings were independently reviewed by two experienced pediatric radiologists in a double-blind manner. In cases of disagreement, a third senior radiologist adjudicated the final interpretation to ensure consistency. Bilateral lung involvement was defined as the presence of consolidation, infiltrates, or reticular patterns in both lungs.

The primary outcome of this study was defined as MPP exacerbation, operationalized as a composite endpoint occurring during hospitalization. Specifically, MPP exacerbation was defined as the occurrence of at least one of the following criteria: the requirement for non-invasive or invasive mechanical ventilation; a significant decrease in the PaO_2/FiO_2 ratio indicating respiratory impairment; the development of imaging-confirmed pleural effusion or the rapid progression of lung consolidation on serial imaging. These criteria were considered clinically relevant indicators of disease exacerbation, and fulfillment of any single criterion was deemed sufficient to classify a case as having experienced exacerbation (such as an "or" composite definition), without applying a hierarchical weighting scheme.

Outcome ascertainment was performed retrospectively based on a comprehensive review of electronic medical records, including clinical notes, laboratory data, and imaging reports throughout hospitalization. To enhance the reliability of outcome classification, two independent senior pediatric clinicians, blinded to model variables, reviewed all cases. In cases of disagreement, a third senior clinician adjudicated the final classification. The same double-blind principle applied to imaging interpretation was extended to outcome assessment to ensure consistency.

Detection of laboratory indicators

All routine laboratory tests were performed within 24 hrs after admission, and key biochemical parameters were reassessed at 72 hrs to evaluate dynamic changes in inflammatory status. Hematological parameters, including white blood cell (WBC) count and lymphocyte percentage, were measured using a Sysmex XN-series automated hematology analyzer (Sysmex Corporation, Kobe, Japan). Biochemical markers, including lactate dehydrogenase (LDH) and D-dimer, were measured using an AU5800 full-automatic biochemistry analyzer (Beckman Coulter Inc., Brea, CA, USA). All assays were conducted using serum or plasma as appropriate for each test, and standard quality control and calibration procedures were strictly followed to ensure the accuracy and reliability of the measurements. Detailed age-specific reference ranges for laboratory parameters used in the present study are provided in Supplementary Table 1.

Measurement of the inflammatory marker C-reactive protein

CRP levels were measured using immunoturbidimetry on AU-series full-automatic biochemistry analyzers (Beckman Coulter Inc., Brea, CA, USA). To assess dynamic changes in the inflammatory response, CRP was measured at admission (CRP_{0hrs}) and approximately 72 hrs after admission (CRP_{72hrs}). ΔCRP% was calculated as a percentage change in CRP levels using the following formula: $\Delta CRP\% = (CRP_{72hrs} - CRP_{0hrs}) / CRP_{0hrs} \times 100\%$. Thus, ΔCRP% represents the percentage-point change in CRP over 72 hrs. For regression analyses, ΔCRP% was scaled *per* 10 percentage-point increase to improve interpretability of effect estimates. A positive ΔCRP% indicates persistence or an increase of inflammation, whereas a negative value reflects a decline.

Detection of immunoglobulin G subclasses as immunological indicators

Serum IgG subclasses (IgG1, IgG2, IgG3, and IgG4) were measured using immunonephelometry on a BN-series nephelometer (Mindray® Bio-Medical Electronics Co., Ltd., Shenzhen, China). The testing results were evaluated against

age-stratified reference intervals provided by the manufacturer for the BN-series system, which are routinely applied in clinical laboratory practice. Specifically, age-specific lower limits of normal were used for each IgG subclass, and patients were classified as having "low" levels if their measured values fell below the corresponding age-adjusted threshold. Given the wide age range of the study population (1–16 years), the detailed age-stratified reference intervals used for classification are provided in Supplementary Table 2 to ensure transparency and reproducibility. A low IgG1 level was considered an important marker of impaired humoral immunity reserve and was incorporated as a key immunological predictor in EM. Measurement of IgG subclasses facilitates assessment of immune function in pediatric patients and enables exploration of their potential associations with the risk of disease exacerbation.

Construction of logistic regression prediction models

Prediction models for the risk of MPP exacerbation in children were developed using a logistic regression framework, including BM and EM. Prior to model construction, the linearity assumption between continuous predictors and the logit of the outcome was evaluated using the Box-Tidwell test and visual inspection of locally weighted scatterplot smoothing (locally estimated scatterplot smoothing – LOESS) curves. The results indicated that most continuous variables, including lymphocyte percentage, LDH, and D-dimer, approximately satisfied the linearity assumption. For ΔCRP%, although mild deviation from strict linearity was suggested by exploratory analysis and SHapley Additive exPlanations (SHAP) plots, the relationship was considered approximately linear within the main data range; therefore, it was retained as a continuous variable in the logistic regression model for interpretability. No variables required transformation using restricted cubic splines or categorization. Given the potential for nonlinearity, ΔCRP% was additionally scaled *per* 10 percentage-point increase to improve model stability and interpretability of the regression coefficients. Moreover, the variables with significant multicollinearity (variance inflation factor > 5) were excluded or combined.

BM included routine clinical and laboratory variables, including age, fever duration, WBC count, lymphocyte percentage, LDH, D-dimer levels, and extent of imaging involvement (unilateral/bilateral). Based on this model, two additional predictors, namely ΔCRP% and IgG1_low (0/1), were incorporated to construct EM. EM was developed to assess the incremental predictive value of dynamic inflammatory changes and humoral immune reserve in estimating the risk of MPP exacerbation. Model performance was comprehensively assessed in terms of discrimination, calibration, and clinical utility. Furthermore, to explore potential nonlinear effects and interactions among predictors, the eXtreme Gradient Boosting (XGBoost) algorithm combined with SHAP was employed to enhance interpretability and validate the robustness of the findings. Model performance was evaluated using receiver operating characteristic (ROC) curve analysis. The area under the curve (AUC), sensitivity, and specificity were calculated and compared between the two models. Differences in AUC were assessed using the DeLong test.

Goodness-of-fit and calibration performance of the logistic regression model

Model fit was assessed using the Hosmer-Lemeshow goodness-of-fit (HL test). Calibration performance was evaluated using calibration curves, calibration slopes, and intercepts to examine the agreement between predicted probabilities and observed event rates.

Decision curve analysis

Decision curve analysis (DCA) was performed to evaluate the clinical net benefit of the models across a range of threshold probabilities. The performance of EM, BM, and "Treat All"/"Treat None" strategies was compared to assess their clinical utility. Models demonstrating higher net benefit across a broader range of thresholds were considered to have greater clinical applicability.

Internal validation of the enhanced model

The stability and generalization ability of EM were evaluated using bootstrap resampling (1,000 resamples). For each resampling, the model was reconstructed, and the AUC was calculated, generating an empirical distribution of AUC values and enabling estimation of a bootstrap-corrected AUC. This procedure was applied to reduce optimism bias and mitigate the impact of overfitting on performance estimates. Model calibration was further assessed using the Brier score as a measure of overall prediction error, with lower values indicating better calibration and more accurate probability estimates.

Risk stratification analysis of the enhanced model

Patients were categorized into three risk groups according to the predicted probabilities generated by EM: low-risk (< 0.20), medium-risk (0.20–0.35), and high-risk (≥ 0.35). Observed incidence rates of MPP exacerbation were compared across these groups to evaluate the model's risk stratification performance and clinical interpretability. A progressive increase in event rates across risk categories was considered indicative of effective risk discrimination, supporting the use of the model for risk-adapted clinical management.

Establishment of a nonlinear model and analysis of interpretability (XGBoost + SHAP)

In the present study, an XGBoost-based nonlinear prediction model was developed to validate the robustness of incremental indicators (ΔCRP% and IgG1_low) and to explore potential nonlinear effects. Model hyperparameters were optimized using 5-fold cross-validation, so as to enhance generalizability. Following model training, the SHAP framework was applied to quantify the contribution and im-

portance of individual features. SHAP summary plots were generated to illustrate the global ranking of feature importance. In addition, SHAP dependence plots were used to evaluate the marginal effects of key variables (such as ΔCRP% and IgG1_low) at different values and to explore their interactions with other predictors, such as lymphocyte percentage and LDH. This approach complements the logistic regression model by capturing complex nonlinear relationships and interaction patterns, thereby improving model interpretability and supporting the biological plausibility of the identified predictors.

Statistical analysis

All statistical analyses were performed using SPSS version 26.0 and Python version 3.10. The distribution of continuous variables was assessed using the Shapiro-Wilk normality test. Normally distributed variables are presented as mean ± standard deviation and were compared using the independent-samples *t*-test. Non-normally distributed variables are expressed as median (interquartile range – IQR) and were compared using the Mann-Whitney *U* test. Categorical variables are presented as frequencies (percentages) and were compared using the χ^2 test or Fisher's exact test, as appropriate. Variables with $p < 0.10$ in univariate analysis were entered into multivariate logistic regression analysis. Independent predictors were identified using a bidirectional stepwise selection procedure. All statistical tests were two-sided, and $p < 0.05$ was considered statistically significant.

Results

Comparison of clinical baseline characteristics and laboratory features in pediatric patients

A total of 512 pediatric patients with confirmed MPP were included in this study, of whom 110 (21.5%) experienced exacerbation. Compared with the non-exacerbation group, patients in the exacerbation group were younger, had a longer duration of fever, and exhibited a higher proportion of bilateral lung involvement ($p < 0.05$). Laboratory findings showed that WBC count, LDH, and D-dimer levels were elevated, whereas lymphocyte percentage was lowered in the exacerbation group. A significant difference in the magnitude of CRP dynamic percentage change (ΔCRP%) was observed ($p < 0.001$), indicating that a persistent inflammatory response is closely associated with disease exacerbation. Disease immunological indicators, low IgG1 and IgG4 levels, were more frequently observed in the exacerbation group ($p < 0.01$), whereas no significant differences were found for IgG2 and IgG3 levels. Moreover, patients in the exacerbation group had longer hospital stays and a higher rate of corticosteroid use ($p < 0.001$) (Table 1). Overall, age, duration of fever, extent of radiological involvement, dynamic changes in CRP, and abnormalities in IgG subclasses were significantly associated with MPP exacerbation and were, therefore, considered candidate predictors for subsequent model development.

Table 1

Baseline features of enrolled children

Variable	Groups		Statistical value	*p*-value
	non-exacerbation (n = 402)	exacerbation (n = 110)		
Age, years	6.6 ± 2.7	5.7 ± 3.1	$t = 2.54$	0.012
Male	218 (54.2)	66 (60.0)	$\chi^2 = 1.16$	0.28
Duration of fever before admission, days	6.1 ± 2.0	7.1 ± 2.6	$t = 3.81$	< 0.001
Bilateral lung involvement	104 (25.9)	60 (54.5)	$\chi^2 = 32.7$	< 0.001
History of wheezing	61 (15.2)	15 (13.6)	$\chi^2 = 0.17$	0.68
WBC count, $\times 10^9$/L	8.4 ± 3.4	9.8 ± 4.0	$t = 2.97$	0.003
Lymphocyte, %	33.9 ± 12.8	27.3 ± 12.5	$t = 4.11$	< 0.001
LDH, U/L	345 (275–416)	427 (360–512)	$Z = 4.55$	< 0.001
D-dimer, mg/L	0.55 (0.35–0.88)	0.97 (0.63–1.65)	$Z = 4.27$	< 0.001
CRP_{0hrs}, mg/L	43.2 ± 26.5	63.5 ± 30.4	$t = 6.05$	< 0.001
ΔCRP%	-33.8 ± 38.9	+8.9 ± 47.1	$t = 7.71$	< 0.001
Low levels, g/L				
IgG1	47 (11.7)	31 (28.2)	$\chi^2 = 15.6$	< 0.001
IgG2	38 (9.5)	18 (16.4)	$\chi^2 = 3.99$	0.046
IgG3	27 (6.7)	7 (6.4)	$\chi^2 = 0.01$	0.91
IgG4	26 (6.5)	16 (14.5)	$\chi^2 = 7.62$	0.006
Glucocorticoid use	60 (14.9)	44 (40.0)	$\chi^2 = 33.3$	< 0.001
Length of hospital stay, days	7 (6–9)	11 (9–15)	$Z = 7.92$	< 0.001

WBC – white blood cell; LDH – lactate dehydrogenase; CRP – C-reactive protein; IgG – immunoglobulin G; n – number of patients.

Values are given as numbers (percentages) or mean ± standard deviation, except for length of hospital stay, LDH, and D-dimer, which are expressed as median (interquartile range).

***Note*: Reference ranges for D-dimer and CRP for all pediatric ages: < 0.5 mg/L, < 8 mg/L, respectively. Other reference ranges are shown in Supplementary Table 1.**

Results of univariate and multivariate logistic regression analyses

All continuous variables were assessed for linearity with the logit prior to modeling. Most variables approximately satisfied the linearity assumption. Although ΔCRP% showed mild deviation from strict linearity, it was considered approximately linear within the main data range and was, therefore, retained as a continuous variable. Univariate analysis showed that age, duration of fever, bilateral lung involvement, WBC count, lymphocyte percentage, LDH, D-dimer, ΔCRP%, and low IgG1 and IgG4 levels were significantly associated with MPP exacerbation ($p < 0.05$). Variables with $p < 0.10$ in univariate analysis were entered into multivariate logistic regression. Duration of fever [odds ratio (OR) = 1.18, 95% confidence interval (CI): 1.05–1.34, $p = 0.007$], bilateral lung involvement (OR = 2.41, 95% CI: 1.45–4.01, $p = 0.001$), lymphocyte percentage (OR = 0.97, 95% CI: 0.95–0.99, $p = 0.008$), LDH (OR = 1.003, 95% CI: 1.001–1.006, $p = 0.012$), D-dimer (OR = 1.79, 95% CI: 1.05–3.06, $p = 0.032$), ΔCRP% (*per* 10 percentage-point increase) (OR = 1.22, 95% CI: 1.08–1.38, $p = 0.001$), and low IgG1 (OR = 2.15, 95% CI: 1.18–3.94, $p = 0.012$) were identified as independent predictors of MPP exacerbation in children (Table 2).

Glucocorticoid use, as an intervention-related variable, was excluded from the primary prediction model because corticosteroid administration was a post-admission treatment decision potentially influenced by early clinical severity assessment. To evaluate potential confounding by indication, sensitivity analyses were additionally performed. After further adjustment for glucocorticoid use as a covariate, ΔCRP% (adjusted OR = 1.19, 95% CI: 1.05–1.35, $p = 0.006$) and low IgG1 status (adjusted OR = 2.02, 95% CI: 1.10–3.73, $p = 0.024$) remained independently associated with MPP exacerbation. Similar findings were observed after excluding patients who received glucocorticoid therapy during hospitalization, with no material changes in model discrimination or effect estimates, supporting the robustness of the primary model.

Discriminating performance of logistic regression models

To evaluate model discrimination, BM and EM were constructed for comparison. BM incorporated routine clinical variables, such as age, duration of fever, WBC count, lymphocyte percentage, LDH, D-dimer, and extent of radiological involvement. EM further incorporated ΔCRP% and low IgG1 status (IgG1_low). ROC analysis showed that both models demonstrated good discriminative performance for predicting MPP exacerbation in children. BM achieved an AUC of 0.792 (95% CI: 0.743–0.838), sensitivity of 73.6%, and specificity of 71.2%. EM showed improved performance, with an AUC of 0.873 (95% CI: 0.835–0.908), sensitivity of 82.7%, and specificity of 80.4% (Figure 1). The difference in AUC between the two models was 0.083 ($p = 0.004$), indicating that the inclusion of ΔCRP% and low IgG1 significantly improved model discrimination. These findings suggest that dynamic inflammatory changes and humoral immune dysfunction provide additional predictive value for MPP exacerbation in children.

Goodness-of-fit and calibration performance of logistic regression models

To further evaluate the agreement between predicted probabilities and observed event rates, the HL test and calibration curves were applied. EM yielded an HL test *p*-value of 0.72, indicating adequate model fitting. Similarly, BM

Table 2

Results of univariate and multivariate logistic regression analyses for MPP exacerbation in children

Variable	OR of univariate analysis (95% CI)	*p*-value	OR of multivariate analysis (95% CI)	*p*-value
Age, years	0.89 (0.82–0.96)	0.003	0.92 (0.84–1.01)	0.074
Duration of fever, days	1.32 (1.17–1.49)	< 0.001	1.18 (1.05–1.34)	0.007
Bilateral lung involvement	3.49 (2.25–5.40)	< 0.001	2.41 (1.45–4.01)	0.001
WBC count, $\times 10^9$/L	1.09 (1.03–1.16)	0.004	1.05 (0.98–1.13)	0.165
Lymphocyte, %	0.95 (0.93–0.97)	< 0.001	0.97 (0.95–0.99)	0.008
LDH, U/L	1.006 (1.004–1.009)	< 0.001	1.003 (1.001–1.006)	0.012
D-dimer, mg/L	2.84 (1.83–4.41)	< 0.001	1.79 (1.05–3.06)	0.032
Initial CRP level, mg/L	1.02 (1.01–1.03)	< 0.001	–	–
ΔCRP% (*per* 10 percentage-point increase)	1.31 (1.19–1.45)	< 0.001	1.22 (1.08–1.38)	0.001
Low levels, g/L				
IgG1	2.96 (1.72–5.08)	< 0.001	2.15 (1.18–3.94)	0.012
IgG4	2.44 (1.19–4.98)	0.015	1.89 (0.92–3.87)	0.083
Glucocorticoid use	3.91 (2.44–6.27)	< 0.001	–*	–*

MPP – *Mycoplasma pneumoniae* pneumonia; OR – odds ratio; CI – confidence interval; WBC – white blood cell; LDH – lactate dehydrogenase; CRP – C-reactive protein; IgG – immunoglobulin G.

***Note*: *Glucocorticoid use as an intervention-related variable was excluded from the prediction model. The multivariate model was constructed using bidirectional stepwise regression, incorporating variables with $p < 0.10$ identified in univariate analysis. For reference ranges for laboratory parameters, see Table 1 and Supplementary Table 1.**

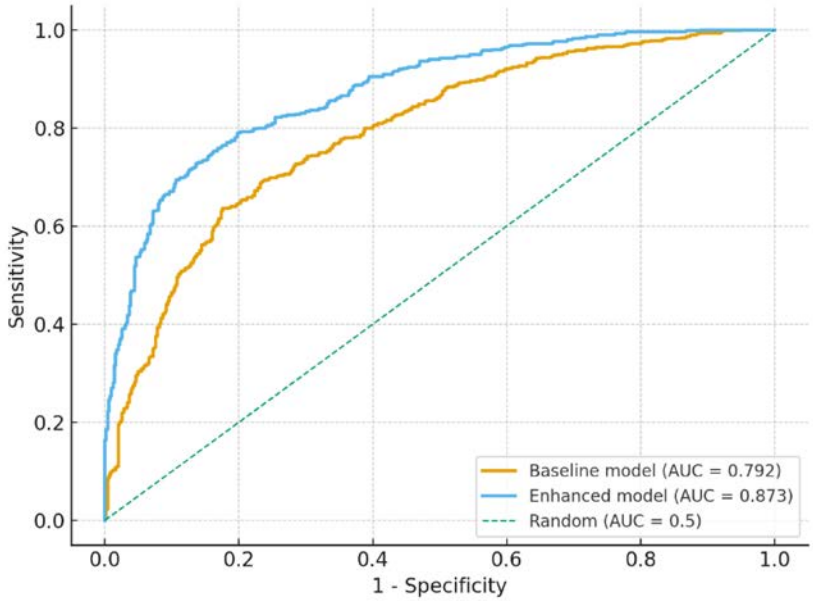

Fig. 1 – Comparison of receiver operating characteristic curves for the discriminating performance of logistic regression models.
AUC – area under the curve.

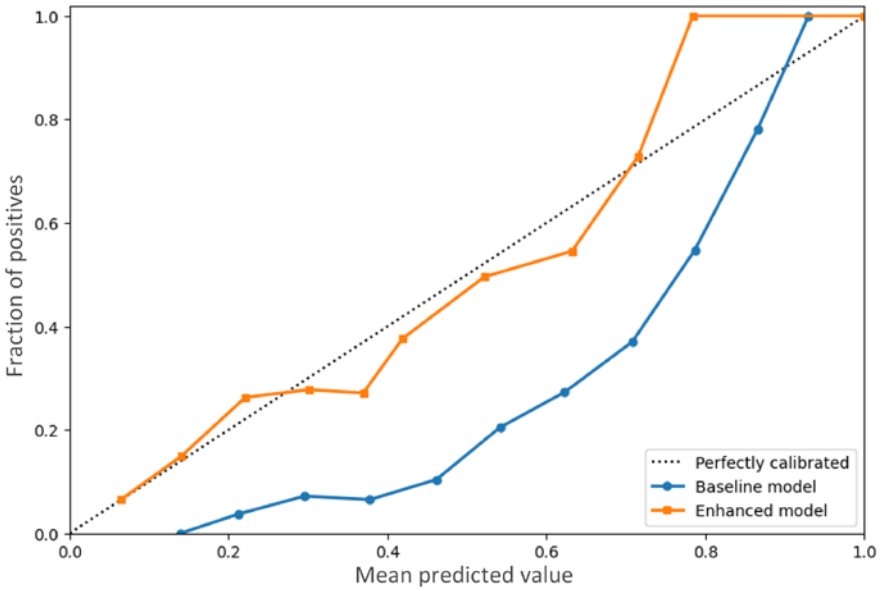

Fig. 2 – Comparison of calibration curves of logistic regression models.

showed a *p*-value of 0.41, which also indicates acceptable calibration with no evidence of poor fit. In both models, predicted probabilities generally increased with higher observed risk of severe disease. However, the calibration curve of EM was closer to the ideal reference line, indicating better agreement between predicted and observed outcomes. By contrast, BM demonstrated a tendency to underestimate risk in the medium-to-high probability range. Compared with BM, EM demonstrated improved calibration performance, as reflected by a calibration slope closer to 1 and an intercept closer to 0, indicating better agreement between predicted and observed risks across the full range of probabilities. Overall, although both models demonstrated acceptable calibration based on the HL test, EM showed superior calibration characteristics based on graphical assessment and calibration metrics, supporting its greater reliability for early risk stratification in clinical practice (Figure 2).

Decision curve analysis results of logistic regression models

DCA was performed to evaluate the clinical net benefit of the prediction models across a range of threshold probabilities. Within the threshold probability range of 0.1–0.7, EM consistently demonstrated higher net benefits than BM as well as the "Treat All" and "Treat None" strategies, indi-

cating superior clinical utility across a broad range of decision thresholds. Notably, EM showed the greatest improvement in net benefit within the 0.2–0.5 threshold range, suggesting that the inclusion of ΔCRP% and IgG1_low substantially enhances the model's clinical applicability (Figure 3). Overall, EM not only improved discriminative performance but also reduced potential clinical harm associated with overtreatment and missed diagnoses, thereby providing more practical support for risk stratification and individualized management of MPP exacerbation in children.

Results of internal validation of the enhanced model

Internal validation of EM was performed with 1,000 bootstrap resamples. The median bootstrap-corrected AUC was 0.823 (95% CI: 0.785–0.865), which was consistent with the apparent AUC, indicating a low risk of overfitting (Figure 4A). Calibration curves demonstrated excellent agreement between predicted probabilities and observed event rates. The model showed strong calibration in the low- and medium-risk ranges, with a slight overestimation in the high-risk group. However, the overall trend remained close to the ideal reference line (Figure 4B). The Brier score of the model was 0.114, further confirming good calibration performance and overall predictive accuracy.

Stratification results of the enhanced model-predicted risks

Applying the stratification into three groups according to model-predicted probabilities, the observed incidence of MPP exacerbation was approximately 10% in the low-risk

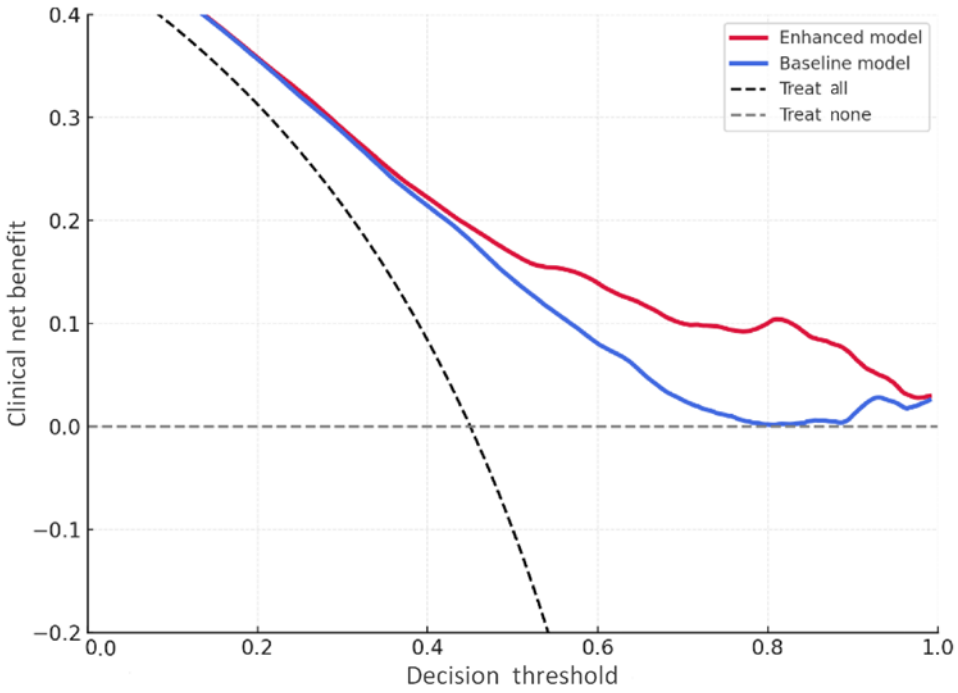

Fig. 3 – Decision curve analysis results of logistic regression models.

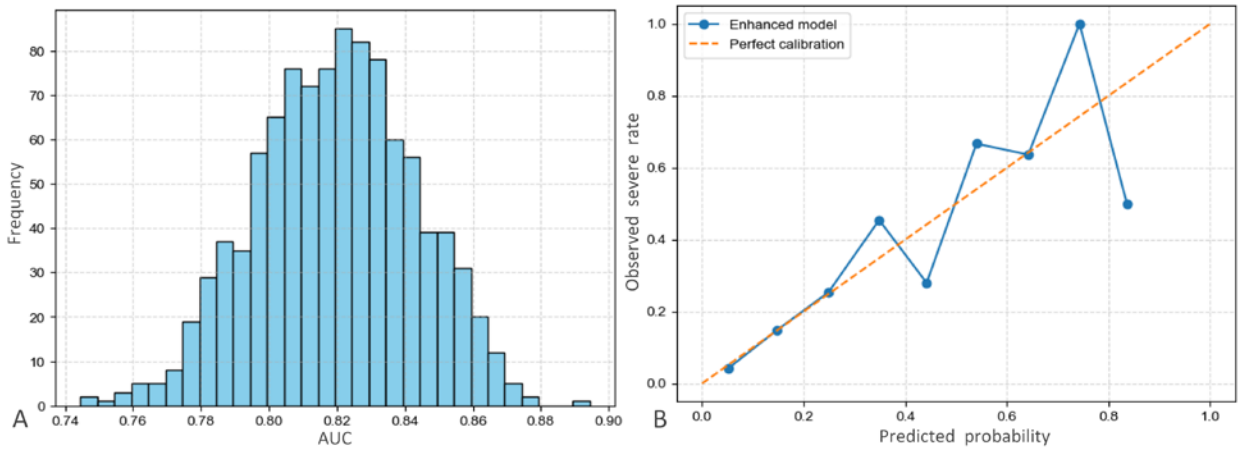

Fig. 4 – Results of internal validation of enhanced model: A) bootstrap distribution of area under curve (AUC) (1,000 resamples); B) calibration curve.

group, which was substantially lower than the overall rate. The incidence increased to approximately 30% in the medium-risk group and further increased to around 50% in the high-risk group, consistent with the model-predicted trends. A clear stepwise increase in event rates was observed across the three risk groups, indicating good discriminatory ability of the model for identifying patients at different levels of exacerbation risk. Notably, the high-risk group exhibited an exacerbation rate of nearly 50%, highlighting its clinical relevance for identifying patients who may benefit from early intervention or closer monitoring. In contrast, the low-risk group showed a markedly lower risk, supporting the potential to reduce unnecessary treatments or imaging examinations in this population (Figure 5).

Nonlinear XGBoost model and SHAP interpretability analysis

To further examine the robustness of key predictors and enhance model interpretability, a nonlinear classification model based on XGBoost was developed using the same feature set as the enhanced logistic model. The XGBoost algorithm can automatically capture nonlinear relationships and higher-order interactions among variables, thereby complementing the limitations of linear logistic regression models in modeling complex feature contributions. SHAP analysis was subsequently applied to interpret the model. The XGBoost model exhibited good predictive performance during 5-fold cross-validation, with a mean AUC of 0.851 (95% CI: 0.823–0.884), sensitivity of 80.2%, and specificity of 77.5% (Supplementary Figure 1). These findings indicated acceptable out-of-sample discrimination and supported the reliability of subsequent SHAP-based interpretability analyses.

The SHAP summary plot of the XGBoost model (Figure 6A) was largely consistent with the results of the logistic regression model, identifying lymphocyte percentage, duration of fever, bilateral lung involvement, ΔCRP%, and low IgG1 as key contributors to the prediction of MPP exacerbation. Notably, ΔCRP% and low IgG1 demonstrated more pronounced contributions in the nonlinear model, suggesting that these variables may exert complex, interaction-dependent effects beyond simple linear associations.

SHAP dependency plots further elucidated potential interaction patterns among variables. For ΔCRP%, SHAP values increased markedly in the case of “insufficient decline” or “re-escalation”, indicating that persistent inflammatory activity is strongly associated with a higher risk of exacerbation. This effect was further amplified in the presence of lymphopenia, reflecting a combined effect of increased inflammatory burden and impaired immune response (Figure 6B). For low IgG1 status, SHAP values were consistently higher when IgG1_low = 1, indicating that reduced humoral immune reserve is an important risk factor. This effect was more pronounced in patients with elevated LDH, suggesting a potential synergistic interaction between immune dysfunction and tissue injury (Figure 6C).

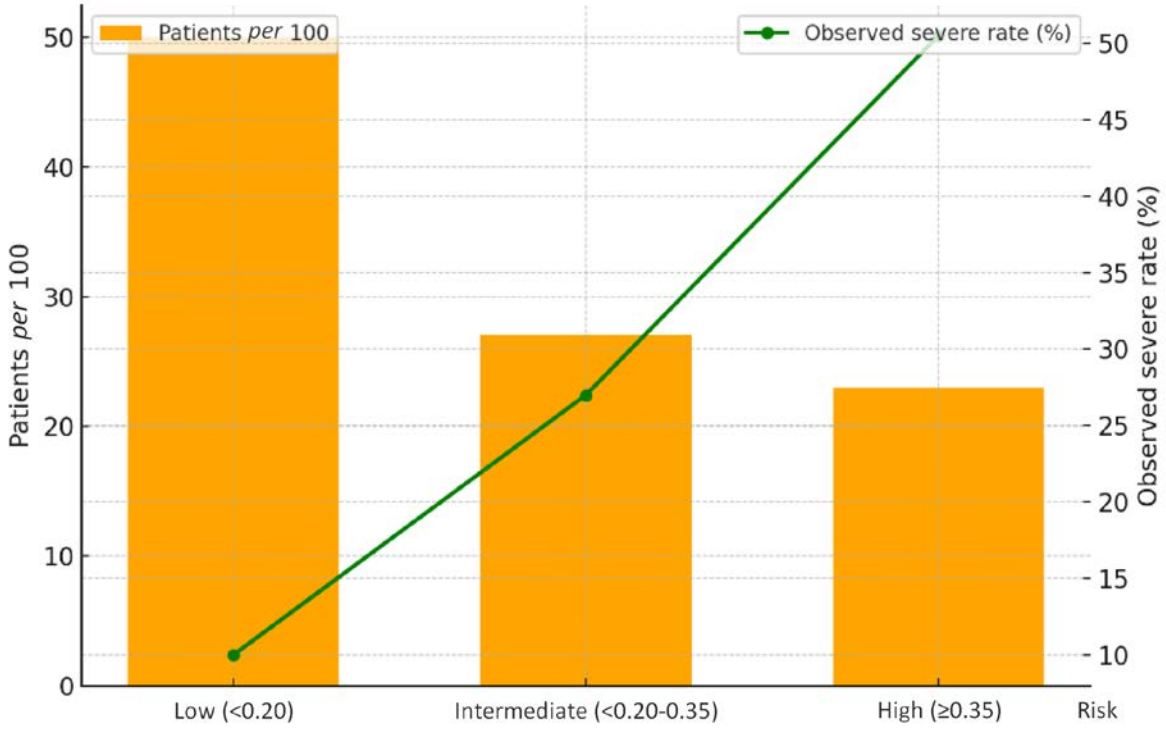

Fig. 5 – Stratification results of the enhanced model-predicted risks.

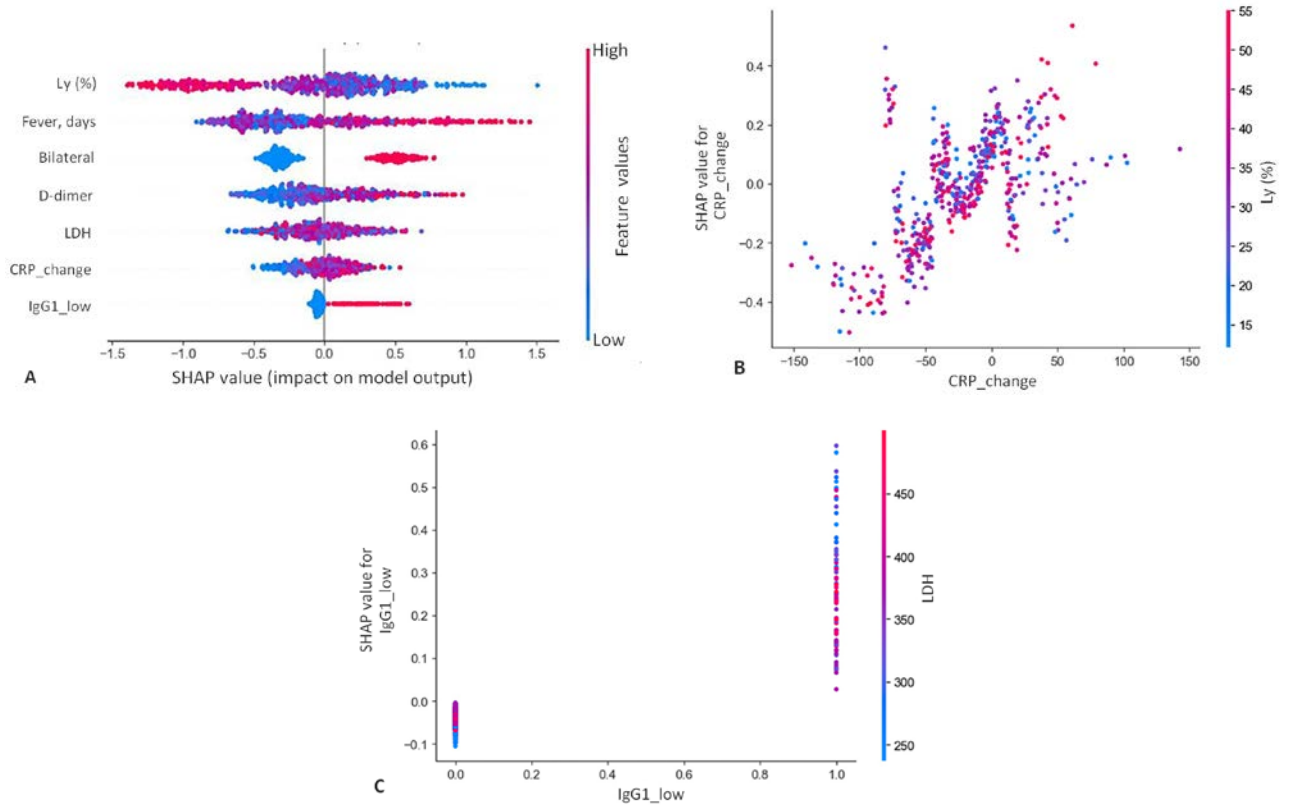

Fig. 6 – Nonlinear XGBoost model and SHAP interpretability analysis results: A) SHAP summary plot of the XGBoost model; B) SHAP dependence plot of CRP change (ΔCRP%); C) SHAP dependence plot of IgG1 low status. XGBoost – eXtreme Gradient Boosting; SHAP – SHapley Additive exPlanations; CRP – C-reactive protein; IgG – immunoglobulin G; Ly – lymphocyte; LDH – lactate dehydrogenase.

Discussion

In the present study, we systematically evaluated the predictive value of ΔCRP% and low IgG1 for disease exacerbation using clinical data from 512 pediatric patients with MPP. Both BM and EM were developed and compared. EM, incorporating ΔCRP% and IgG1_low, demonstrated superior predictive performance compared with BM (AUC = 0.083), along with good model calibration and effective risk stratification.

CRP is a crucial marker of inflammatory response, and its dynamic change (ΔCRP%) may better reflect the persistence and intensity of inflammation than a single measurement [10]. In this study, ΔCRP% made a substantial contribution to EM and showed interactions with lymphocyte percentage and LDH. These findings are consistent with previous research results. For example, Zhang et al. [11] reported that the combined detection of CRP and LDH could serve as a marker of disease severity in pediatric MPP. Besides, Reccardini et al. [12] also uncovered an association between ΔCRP% and disease progression, supporting the relevance of CRP changes in predicting clinical deterioration. The predictive value of ΔCRP% likely lies in its ability to capture the temporal evolution of inflammatory responses, whereas static CRP measurements may not fully reflect the trajectory of disease progression.

IgG1 is a major component of humoral immunity, and reduced levels may impair pathogen clearance and host defense [13]. In our study, low IgG1 was identified as an important contributor to EM and interacted with lymphocyte percentage. Lee et al. [14] reported a 1-year mortality rate of 56% in patients with IgG1 deficiency compared with deficiencies in other IgG subclasses, suggesting its potential prognostic relevance. Moreover, IgG1 deficiency has been associated with increased susceptibility to infections and immune dysregulation [15]. Taken together, these findings suggest that reduced IgG1 levels may contribute to persistent infection and sustained inflammatory responses, thereby increasing the risk of disease exacerbation.

The results of the XGBoost model were largely consistent with those of the enhanced logistic regression model, while additionally revealing nonlinear and interaction effects that cannot be captured by the latter. These findings further support the critical roles of dynamic CRP changes and low IgG1 in the MPP exacerbation in children. The complementary use of these modeling approaches strengthens the robustness of model interpretation and provides mechanistic insight into the clinical significance of persistent inflammation and impaired immune reserve.

EM demonstrated improved discriminative performance and satisfactory calibration, indicating that the inclusion of ΔCRP% and IgG1_low provides incremental predictive val-

ue. This finding is consistent with previous studies emphasizing the advantages of multiparametric models in MPP risk assessment. For instance, Chen et al. [5] showed that composite indicators, such as CRP-neutrophil to lymphocyte ratio (C-NLR) and lymphocyte-CRP ratio (LCR), improved the prediction of refractory MPP. Furthermore, the XGBoost + SHAP analysis in our study revealed potential interactions between ΔCRP%, IgG1_low, and other variables (such as lymphocyte percentage and LDH), suggesting that these factors may jointly influence disease progression. For instance, reduced lymphocyte percentage may reflect immune suppression, while elevated LDH may indicate tissue injury. Their combined effects with ΔCRP% and IgG1_low may contribute to a higher risk of exacerbation [16].

Risk stratification analysis further demonstrated that the observed incidence of severe disease increased from approximately 10% in the low-risk group to nearly 50% in the high-risk group, highlighting the clinical relevance of the model. These findings support the potential utility of early risk identification in guiding clinical management. Jiang et al. [17] reported that early recognition of high-risk patients enables timely adjustment of treatment strategies, such as the use of immunomodulatory therapy or intensified supportive care, thereby improving outcomes. In addition, previous studies have shown that inflammatory biomarkers (such as CRP and IgM) can help predict the complications of MPP, including pleural effusion [18, 19]. Building on this evidence, our study suggests that ΔCRP% and IgG1_low may provide additional value in predicting overall exacerbation risk.

Limitation of the study

Nevertheless, several limitations should be acknowledged. Firstly, this was a single-center retrospective study, and although internal validation using bootstrap resampling (1,000 iterations) was performed, no external validation was conducted. Therefore, the generalizability of the model remains uncertain. Notably, ΔCRP% and IgG1 measurements depend on specific analytical platforms (such as Beckman Coulter AU-series and Mindray® BN-series), and inter-laboratory variability may introduce systematic differences, potentially affecting model performance in other settings. This suggests a moderate risk of limited transportability. Future studies should prioritize external validation in independent multicenter cohorts. In addition, temporal validation (such as training on 2020–2022 data and testing on 2023 data) may provide a more robust assessment of model stability. Standardization of laboratory measurements may further improve model applicability. Secondly, although ΔCRP% and low IgG1 were identified as key predictors, IgG subclass testing is not routinely performed in many pediatric settings, which may limit clinical applicability. Future studies are warranted to explore alternative markers and validate these findings in larger populations.

Conclusion

Ultimately, we developed a prediction model for pediatric *Mycoplasma pneumoniae* pneumonia that demonstrated good discriminative performance, calibration, and risk stratification, with the dynamic percentage change in C-reactive protein and immunoglobulin G1 as key predictors. These findings provide additional insight into the early identification of *Mycoplasma pneumoniae* pneumonia exacerbation and suggest a potential framework for risk assessment integrating inflammatory dynamics and immune status in clinical practice.

Conflict of interest

The authors declare no conflict of interest.

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Supplementary Table 1

Age-specific reference ranges for laboratory parameters used in the present study

Age group, years	WBC, $\times 10^9$/L	Lymphocyte, %	LDH, U/L	IgG1, g/L	IgG2, g/L	IgG3, g/L	IgG4, g/L
1–3	6.0–17.0	50–70	150–450	2.3–6.3	0.4–1.5	0.2–1.2	0.01–0.5
4–6	5.5–15.5	40–60	140–400	3.0–8.0	0.5–2.0	0.3–1.5	0.02–0.8
7–12	4.5–13.5	30–50	120–350	4.0–10.5	0.7–3.0	0.4–1.8	0.03–1.0
13–16	4.0–11.0	20–45	100–300	5.0–12.0	1.0–4.0	0.5–2.0	0.05–1.5

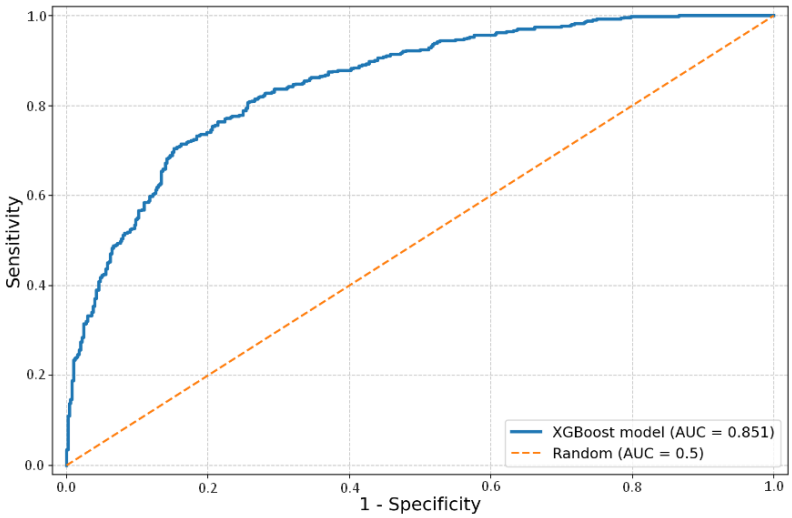
WBC – white blood cell; LDH – lactate dehydrogenase; IgG – immunoglobulin G.

Supplementary Table 2

Age-stratified reference intervals used for classification

Age group, years	IgG1	IgG2	IgG3	IgG4
1–3	2.3–6.3	0.4–1.5	0.2–1.2	0.01–0.5
4–6	3.0–8.0	0.5–2.0	0.3–1.5	0.02–0.8
7–12	4.0–10.5	0.7–3.0	0.4–1.8	0.03–1.0
13–16	5.0–12.0	1.0–4.0	0.5–2.0	0.05–1.5

IgG – immunoglobulin G.
Values are expressed as lower and upper limits of normal for each age group and given as g/L. IgG subclass levels below the lower limit of the corresponding age-specific interval were classified as "low".
Note: **Reference intervals were based on the manufacturer's instructions for the BN-series nephelometer (Mindray® Bio-Medical Electronics Co., Ltd., Shenzhen, China) and were cross-referenced with published pediatric immunoglobulin standards.**



Supplementary Fig. 1 – Receiver operating characteristic curve of the eXtreme Gradient Boosting (XGBoost) model.
AUC – area under the curve.

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Early diagnosis and optimization of intraoperative management strategies for posterior tibial tendon entrapment following ankle fractures in the elderly

Rana dijagnoza i optimizacija intraoperativnih strategija lečenja za uklještenje zadnje tibijalne tetive nakon preloma skočnog zgloba kod starijih osoba

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Abstract

Background/Aim. Posterior tibial tendon (PTT) entrapment is a rare, often underdiagnosed, but severe complication of complex ankle fractures. The aim of the study was to determine the characteristics of PTT entrapment in elderly patients with ankle fractures, and to establish a predictive model based on preoperative available clinical and imaging data. **Methods.** The study enrolled a total of 130 elderly patients treated between 2019 and 2024. Data were retrospectively analyzed, and all patients completed a minimum follow-up period of 12 months. Using intraoperative confirmation as the gold standard, a basic clinical logistic regression (LR) model was compared with an imaging-enhanced LR model (incorporating fracture fragment count and PTT sheath involvement), a random forest (RF) model, and a support vector machine (SVM). Performance was validated *via* 5-fold cross-validation, area under the receiver operating characteristic (ROC) curve (AUC), calibration, and decision curve analysis (DCA). **Results.** PTT entrapment occurred in 29.2% (38/130) of patients, primarily located in the posterior fracture gap (68.4%) or medial malleolus (31.6%). Morphological findings included simple mechanical incarceration (50.0%), soft tissue adhesion (36.8%), and tendon surface injury (13.1%). The imaging-enhanced LR model significantly outperformed the basic model (AUC 0.89 vs. 0.72) and exceeded RF (0.85) and SVM (0.88) models. DCA demonstrated high net benefit across risk levels, and intraoperative findings showed high consistency with imaging-based predictions. **Conclusion.** PTT entrapment is common in elderly ankle fractures. An imaging-enhanced predictive model based on preoperative computed tomography fracture morphology and local anatomy enables effective risk assessment, providing a reliable reference for targeted intraoperative exploration and surgical management strategies.

Keywords:
aged; ankle fractures; diagnosis; models, statistical; prognosis; tendon entrapment.

Apstrakt

Uvod/Cilj. Uklještenje zadnje tibijalne tetive (*posterior tibial tendon* – PTT) predstavlja retku, često nedovoljno prepoznatu, ali ozbiljnu komplikaciju složenih preloma skočnog zgloba. Cilj rada bio je da se utvrde karakteristike uklještenja PTT kod starijih pacijenata sa prelomima skočnog zgloba i da se uspostavi prediktivni model zasnovan na preoperativno dostupnim kliničkim i podacima medicinskih snimanja. **Metode.** U studiju je bilo uključeno ukupno 130 starijih pacijenata lečenih u periodu između 2019. i 2024. godine. Podaci su retrospektivno analizirani, a svi pacijenti su praćeni u minimalno 12 meseci. Koristeći intraoperativnu potvrdu kao zlatni standard, osnovni model logističke regresije (LR) zasnovan na kliničkim podacima upoređen je sa LR modelom unapređenim podacima medicinskih snimanja (koji uključuje broj fragmenata preloma i zahvaćenost omotača PTT), modelom „slučajne šume“ (*random forest* – RF) i algoritmima *support vector machine* (SVM). Učinak je validiran pomoću petostruke unakrsne validacije, površine ispod krive *receiver operating characteristic* (ROC) – AUC, kalibracije i analize krive odlučivanja (*decision curve analysis* – DCA). **Rezultati.** Uklještenje PTT registrovano je kod 29,2% (38/130) pacijenata, primarno lokalizovano u zadnjem delu preloma (68,4%) ili u medijalnom maleolusu (31,6%). Morfološki nalazi uključivali su jednostavno mehaničko uklještenje (50,0%), adheziju mekog tkiva (36,8%) i oštećenje površine tetive (13,1%). Model LR unapređen podacima medicinskih snimanja značajno je nadmašio osnovni model (AUC 0,89 vs. 0,72) i premašio modele RF (0,85) i SVM (0,88). DCA je pokazala visoku neto korist kroz različite nivoe rizika, a

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intraoperativni nalazi bili su u velikoj meri usklađeni sa predikcijama zasnovanim na medicinskim snimcima. **Zaključak.** Uklještenje PTT je česta pojava kod preloma skočnog zgloba kod starijih osoba. Prediktivni model unapređen podacima medicinskog snimanja, zasnovan na preoperativnoj morfologiji preloma dobijenoj kompjuterizovanom tomografijom i lokalnoj anatomiji, omogućava efikasnu procenu rizika, pružajući pouzdanu osnovu za ciljano intraoperativno istraživanje i strategije hirurškog lečenja.

Ključne reči:
stare osobe; skočni zglob, prelomi; dijagnoza; modeli, statistički; prognoza; tetiva, uklještenje.

Introduction

As the population continues to age rapidly, the incidence of ankle fractures (AFs) among the elderly is rising, making it one of the most common lower limb injuries in this age group [1]. Compared to younger patients, elderly individuals are more likely to present with osteoporosis, complex fracture patterns, and poor soft tissue conditions, all of which increase the difficulty of surgical management [2, 3]. Therefore, the treatment objective is not only to achieve stable reduction and internal fixation, but also to minimize the risk of missing critical structural injuries and preventing subsequent postoperative dysfunction [4, 5].

The posterior tibial tendon (PTT) is a key dynamic structure that maintains medial ankle stability and arch integrity and plays an important role in gait, weight-bearing transmission, and coordinated ankle movement [6]. In AFs, particularly those involving the posterior or medial malleolus, the normal course and gliding environment of PTT may be disrupted by displaced fragments, fragment incarceration, or altered anatomical relationships. This may result in entrapment, restricted mobility, or even damage to the tendon surface [7]. However, due to its deep anatomical location, PTT involvement often lacks specific clinical manifestations. Preoperative physical examination and routine imaging provide limited information, leading to frequent underestimation or oversight in clinical practice [8, 9]. Additionally, because of the difficulty in preoperative identification, PTT entrapment is often only recognized intraoperatively when reduction is impeded, or postoperatively when poor reduction, persistent pain, or functional limitations are observed. Missed or delayed diagnosis may require revision surgery and negatively affect recovery [10].

The previous study on PTT entrapment has mainly consisted of case reports or small retrospective series, focusing on intraoperative management rather than systematic risk assessment [11]. In elderly patients, osteoporosis and comminuted fractures further complicate fracture morphology, making abnormal tendon course or entrapment difficult to identify through routine imaging. Reliance on intraoperative exploration alone is, therefore, inherently passive and uncertain. Currently, quantitative studies assessing the risk of PTT entrapment based on preoperative clinical and imaging features are lacking. Moreover, existing studies are largely descriptive, and few have linked predictive findings with intraoperative morphology or surgical complexity, limiting their clinical applicability [12, 13]. Therefore, identifying high-risk patients preoperatively and optimizing intraoperative strategies remains an important but underexplored issue.

Based on this background, the present study systematically analyzed the characteristics of PTT entrapment in elderly patients with AFs and aimed to construct a predictive model using preoperative clinical and imaging data. In addition, intraoperative morphological observations were incorporated to explore the relationship between predictive results and surgical findings, providing a practical approach for preoperative risk assessment and intraoperative management.

Methods

Study design and subjects

This single-center retrospective cohort study consecutively enrolled 130 elderly patients who underwent open reduction and internal fixation for AFs at our hospital between December 2019 and December 2024. Based on intraoperative findings of PTT entrapment, patients were categorized into two groups: the entrapment group and the non-entrapment group. The study protocol was approved by the Ethics Committee of Jiangsu Province Hospital on Integration of Chinese and Western Medicine (from December 20, 2019). Informed consent was waived due to the retrospective study design.

Sample size estimation

Due to the retrospective design of this study, the sample size consisted of all eligible cases consecutively collected during the study period. The primary outcome was the presence or absence of intraoperative PTT entrapment. Following general principles for predictive modeling, the sample size of the logistic regression (LR) model should match the number of candidate predictor variables to ensure the robustness of model estimation. In this study, the number of independent variables was strictly controlled during modeling, and the regularized LR model was used to mitigate overfitting risk. Furthermore, model performance was internally validated using 5-fold cross-validation. Based on the above strategies, the sample size was deemed sufficient for predictive model construction and preliminary validation.

Inclusion and exclusion criteria

Inclusion criteria were as follows: patients aged ≥ 65 years; a diagnosis of isolated malleolar, bimalleolar, or trimalleolar fractures; completion of a preoperative ankle computed tomography (CT) examination; undergoing in-

traoperative exploration of PTT to confirm entrapment; and a postoperative follow-up period of ≥ 12 months.

Exclusion criteria were as follows: patients with a history of severe injury or prior surgery of the ipsilateral ankle joint; concurrent pathological fracture or infectious disease; severe neuromuscular system disease affecting lower limb function; or incomplete imaging or follow-up data.

Collection of baseline clinical variables

Demographic variables included age and sex. Body mass index (BMI) was calculated based on preoperative height and weight. The affected side was recorded. Fracture-related clinical characteristics included fracture type and extent of involvement. Fractures were classified as isolated malleolar, bimalleolar, or trimalleolar based on preoperative imaging assessment. Follow-up duration was defined as the time interval from the date of surgical completion to the last follow-up and was reported in months. Osteoporosis status was determined based on preoperative bone mineral density examination or previous diagnosis. Osteoporosis was defined as a T-value ≤ – 2.5 in patients who underwent dual-energy X-ray absorptiometry [14]. Patients who failed to obtain preoperative bone mineral density values were also classified as osteoporosis if the diagnosis of osteoporosis had been clearly documented in the previous medical record with corresponding treatment.

Collection of preoperative imaging variables

Preoperative imaging variables were derived from routine imaging examinations performed after admission and before surgery, including ankle X-ray and CT scans. All imaging assessments were performed preoperatively and excluded any intraoperative findings. Posterior malleolar fracture involvement was defined as involvement of the posterior tibial margin forming an independent fracture fragment. The number of fracture fragments was assessed. Two physicians experienced in foot and ankle surgery independently interpreted the images without knowledge of surgical outcomes and stratified the findings based on fragment number. For ease of model construction and analysis, stratification results were further classified into two categories, with fragment number ≥ 2 defined as multiple fragments and < 2 as fewer fragments [15]. A positive finding of PTT sheath involvement was defined *via* CT as a fracture line extending into the PTT sheath or a fracture fragment significantly altering the tendon's course, resulting in direct contact or compression.

Definition of outcome variables and intraoperative morphological verification

The outcome was the presence or absence of intraoperative PTT entrapment. During fracture reduction and fixation, an experienced foot and ankle surgeon directly examined PTT to confirm whether it was embedded within the fracture gap or constrained by soft tissue. PTT entrapment was defined as positive if the tendon was located within the fracture gap, formed mechanical incarceration with fracture fragments, or required release/traction to restore normal course. For patients who were confirmed to have PTT entrapment intraoperatively, the following morphological characteristics were further recorded: entrapment site (posterior AF gap, medial malleolus fragment space, etc.) and entrapment pattern (simple mechanical entrapment, concurrent soft tissue adhesion, concurrent tendon surface injury). The above intraoperative findings served as a morphological verification basis for imaging predictive results.

Construction of basic and imaging-enhanced logistic regression predictive models

To construct a control model for predicting the risk of PTT entrapment and avoid potential information leakage, a basic LR model without incorporating imaging enhancement features was first established based on preoperative baseline clinical and fracture morphology variables. Candidate independent variables included age, osteoporosis status, and posterior malleolar fracture involvement. Considering the sample size and event number limitations, L2 regularization was applied to reduce overfitting risk and enhance parameter estimation robustness.

Based on the basic model, preoperative imaging enhancement features, including fracture fragment number stratification and PTT sheath involvement, were further incorporated to construct an imaging-enhanced LR model, used to evaluate the incremental value of imaging structure information for the predictive performance of the model.

To ensure robustness of model performance, all LR models underwent internal validation using 5-fold stratified cross-validation. Within each fold, the model was fitted on the training set and generated predicted probabilities on the corresponding validation set for subsequent discriminatory power, calibration performance, and decision curve analysis (DCA).

Construction of a machine learning predictive model

To verify the predictive consistency of imaging enhancement features across different modeling strategies and serve as performance control, random forest (RF) and support vector machine (SVM) models were further constructed using the same set of preoperative clinical and imaging variables. Given the relatively limited sample size, this study did not employ complex nested cross-validation or large-scale parameter search. Instead, models were constructed using preset conventional parameter settings to reduce the risk of overfitting and enhance model reproducibility. The RF model used a fixed number of decision trees and limited the maximum depth of a single tree. The SVM model used a radial basis function kernel and default penalty parameters. Consistent with the LR models, RF and SVM models also underwent internal validation using 5-fold stratified cross-validation. The predict-

ed probabilities generated by each model during cross-validation were used for uniform performance evaluation and comparison.

Evaluation of discriminatory power and classification performance of predictive models

The discriminatory power of models was assessed using receiver operating characteristic (ROC) curves, with area under the curve (AUC) as the primary metric for the capability of the model to distinguish patients with and without PTT entrapment. With the predicted probability threshold uniformly set at 0.5, the sensitivity, specificity, and overall accuracy of each model were calculated.

Calibration performance evaluation

For the final selected imaging-enhanced LR model, its calibration performance for predicted probability was evaluated. Calibration performance measured the consistency between the model's predicted probability of PTT entrapment occurrence and the actual incidence rate. The model's predicted probabilities were grouped by magnitude, and the mean predicted probability and corresponding actual incidence rate were calculated for each group. They were graphically compared against the ideal calibration curve to visually illustrate the model's calibration across different risk intervals. Meanwhile, the Brier score was employed to quantitatively assess the model's overall calibration performance. The Brier score was defined as the mean of the squared differences between predicted probabilities and actual outcomes.

Decision curve analysis

To assess the potential value of the imaging-enhanced LR model in clinical decision-making, the model was further evaluated using DCA. Using DCA, the clinical utility of the imaging-enhanced LR model was assessed by comparing the net benefit of different decision strategies across a range of threshold probabilities. The threshold probability represented the clinical risk threshold for further intraoperative exploration or intervention. When the predicted probability was higher than this threshold, intervention was considered justified. Net benefit calculation comprehensively considered both true positive and false positive results and was defined as the trade-off between the benefit of correctly identifying events and the cost of unnecessary interventions at a given threshold probability.

Interpretability analysis

To elucidate the predictive contribution of each variable in the imaging-enhanced LR model, standardized regression coefficients and their corresponding odds ratios (OR) were examined. Continuous variables were normalized prior to model fitting to ensure comparability of coefficients. Regression coefficients and OR were used to assess the direction, magnitude, and strength of association between predictors and the outcome.

Risk stratification and intraoperative grading processing algorithms

Based on the predicted probabilities generated by the imaging-enhanced LR model, subjects underwent preoperative risk stratification. Patients were categorized into low-, medium-, and high-risk groups according to preset probability thresholds, reflecting their relative risk of PTT entrapment. This risk stratification was conducted based solely on preoperative information and did not incorporate any intraoperative findings. Based on preoperative risk stratification, an intraoperative grading algorithm was constructed by considering direct observation of the PTT status intraoperatively. Intraoperative grading was completed mainly based on the presence or absence of PTT entrapment, its severity, and the integrity of the tendon and surrounding soft tissue. The entrapment was divided into grades 0–3. Grade 0 (no entrapment): no PTT entering the fracture gap was found intraoperatively, and the tendon ran naturally without obvious traction or obstruction. Grade 1 (mild and reversible entrapment): PTT was partially embedded in the fracture gap or obscured by soft tissue, but without obvious adhesion. After mild traction or partial release, it could be successfully reduced without structural damage. Grade 2 (deep entrapment with soft tissue adhesion): PTT was deeply embedded in the fracture gap of the posterior ankle or medial ankle, often accompanied by obvious soft tissue adhesion, and it was difficult to release the entrapment by simple traction. Grade 3 (entrapment + tendon injury): abrasions, partial tear, or structural integrity of the PTT surface was visible during the process of release. Grading assessment was performed by the surgeon during fracture reduction and fixation and was used to standardize intraoperative assessment and treatment procedures. Through this approach, the results of preoperative risk stratification were linked with the intraoperative grading process to explore the feasibility of preoperative assessment based on predictive models in guiding intraoperative decision-making.

Statistical analysis

Statistical analysis was performed using Python 3.11 software, primarily relying on statistical and machine learning analysis libraries such as SciPy and scikit-learn. The *t*-test was used for intergroup comparisons regarding continuous variables. Categorical variables were analyzed using the Chi-square test. The level of statistical significance was defined for $p < 0.05$.

Results

Baseline data

This study included 130 elderly patients with AFs, with a mean age of 70.30 ± 6.10 years. Intraoperative findings confirmed PTT entrapment in 38 (29.2%) cases. Bimalleolar

and trimalleolar fractures were predominant, accounting for 43.1% and 35.4%, respectively. The mean follow-up time was 16.80 ± 4.30 months. There was no significant difference between the entrapment and non-entrapment groups. As to baseline characteristics, age, sex, body mass index (BMI), injury side, and fracture type showed no statistically significant differences between the two groups ($p > 0.05$). The incidence rate of osteoporosis in the entrapment group was significantly higher than in the non-entrapment group ($p < 0.05$). In addition, the proportion of patients with posterior AFs and those with a fracture line extending into the PTT sheath on preoperative CT was significantly higher in the entrapment group ($p < 0.05$). A representative preoperative axial CT image demonstrating PTT involvement is shown in Figure 1. The fracture fragment extended into the retromalleolar groove and altered the normal anatomical course of the PTT, resulting in direct compression and potential entrapment. Except for the above factors, there was no statistically significant difference between the two groups in the other baseline clinical characteristics (Table 1).

Intraoperative morphological characteristics of posterior tibial tendon entrapment

A total of 38 patients with intraoperatively confirmed PTT entrapment were documented. Entrapment occurred most frequently in posterior AFs [26 (68.4%)], followed by the medial malleolus fragment [12 (31.6%)]. No PTT entrapment anterior to the tibiotalar joint or at the level of the talonavicular joint was observed.

Nineteen (50.0%) cases showed simple mechanical incarceration of the tendon, with complete continuity of the tendon and no obvious abnormality of the surrounding soft tissue. Fourteen (36.8%) patients exhibited varying degrees of concurrent soft tissue adhesions, presenting as limited tendon mobility while maintaining structural integrity. Additionally, 5 (13.1%) cases had concurrent fiber abrasion or focal injury on the tendon surface during release, but no complete rupture was found. All cases of PTT entrapment were treated intraoperatively, and there was no failure of fracture reduction or need to terminate surgery due to PTT entrapment.

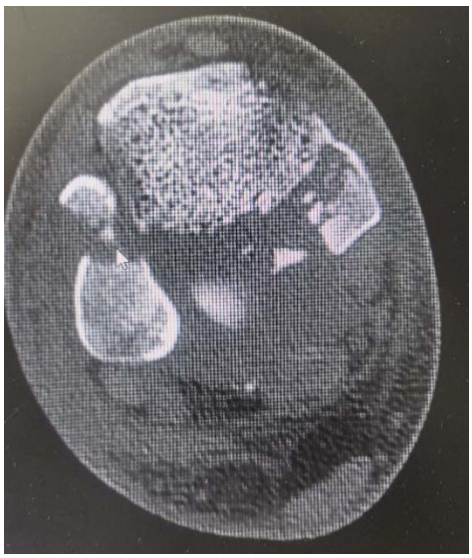

Fig. 1 – Representative preoperative axial computed tomography image demonstrating posterior tibial tendon involvement (arrow).

Table 1

Baseline data

Variable	Group		t/χ^2	*p*-value
	entrapment (n = 38)	non-entrapment (n = 92)		
Age, years	71.34 ± 6.25	69.87 ± 5.93	1.265	0.208
Female	24 (63.1)	54 (58.7)	0.223	0.637
BMI, kg/m²	24.18 ± 2.87	23.62 ± 2.54	1.100	0.273
Left-sided injury	20 (52.6)	46 (50.0)	0.075	0.785
Fractures				
isolated malleolar	6 (15.8)	22 (23.9)	1.050	0.305
bimalleolar	16 (42.1)	40 (43.5)	0.021	0.886
trimalleolar	16 (42.1)	30 (32.6)	1.061	0.303
Osteoporosis	21 (55.3)	30 (32.6)	5.789	0.016
Posterior ankle fracture	30 (79.0)	39 (42.4)	14.430	< 0.001
Fracture line extending into tendon sheath	23 (60.5)	24 (26.1)	13.818	< 0.001
Follow-up duration, months	16.95 ± 4.56	16.78 ± 4.23	0.204	0.839

BMI – body mass index; n – number.

Values are given as numbers (percentages) or mean ± standard deviation.

Predictive results for posterior tibial tendon entrapment using a basic logistic regression model without incorporating imaging enhancement features

The ROC curve analysis showed that the basic LR model without imaging enhancement features achieved an AUC of 0.72, suggesting that the model has moderate and relatively robust discriminatory power (Figure 2). In the model coefficient analysis, posterior AF involvement was the main predictor of PTT entrapment, with a standardized regression coefficient of 1.56 and a corresponding OR of 4.78, suggesting that patients with posterior AFs have a significantly elevated risk of tendon entrapment. Age (OR = 0.57) and osteoporosis (OR = 0.69) were included as adjustment variables in the model, and their effects were attenuated after controlling for fracture morphology.

Comparison of the imaging-enhanced logistic regression model with machine learning models for performance in predicting posterior tibial tendon entrapment

The ROC curve analysis revealed that the discriminatory power of the imaging-enhanced LR model was significantly improved compared with the basic model, achieving an AUC of 0.89, significantly higher than that of the LR model without imaging enhancement features (AUC = 0.72). The RF and SVM models also showed high discriminatory power with AUCs of 0.85 and 0.88, respectively (Figure 3). The classification performance of each model was further evaluated at a fixed predicted probability threshold of 0.5. The results showed that the imaging-enhanced LR model showed a balanced performance between sensitivity (71.1%) and specificity (94.6%), with an overall accuracy of 87.7%. The RF model had relatively high sensitivity (78.9%), but its overall discriminatory power and robustness did not significantly outperform the imaging-enhanced LR model. Although the SVM model achieved the highest specificity (100%) and accuracy (91.5%), its sensitivity did not improve further, and the classification results showed a more extreme distribution pattern. Considering the discriminatory power, classification performance, and model interpretability, the imaging-enhanced LR model demonstrated better robustness and clinical interpretability while maintaining higher predictive performance. Therefore, this model was selected as the primary predictive model for subsequent risk stratification, interpretability analysis, and clinical decision-making processes.

Calibration performance of the imaging-enhanced logistic regression model for predicting posterior tibial tendon entrapment

The calibration curve demonstrated good agreement between the predicted risk and the observed incidence of PTT entrapment across most probability intervals (Figure 4). Although the model's predicted probability was slightly lower than the observed incidence rate in the low-risk interval, the overall trend was generally consistent with the ideal calibration line, with no significant systematic overestimation or underestimation observed. The Brier score was 0.097, indicating acceptable model accuracy and robustness at the predicted probability level. These results indicate that the imaging-enhanced LR model not only possesses good discriminatory power but also has reliable risk estimation performance, providing a basis for subsequent risk stratification and clinical decision-making.

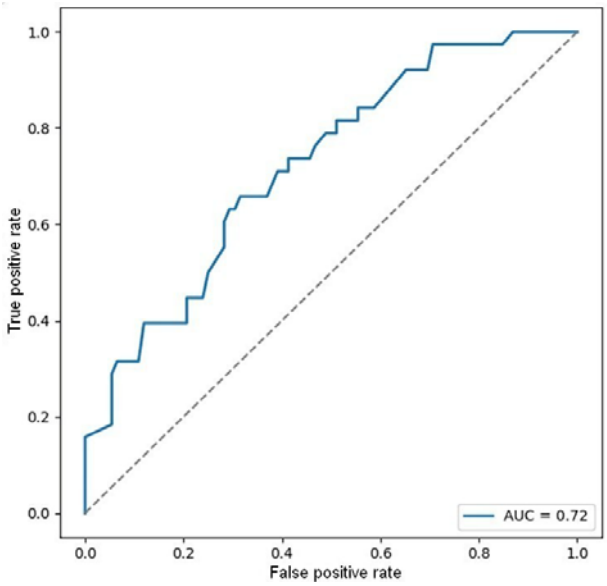

Fig. 2 – Receiver operating characteristic curve for basic clinical logistic regression model without incorporating imaging enhancement features. Dashed lines represent reference lines for random classification. AUC – area under the curve.

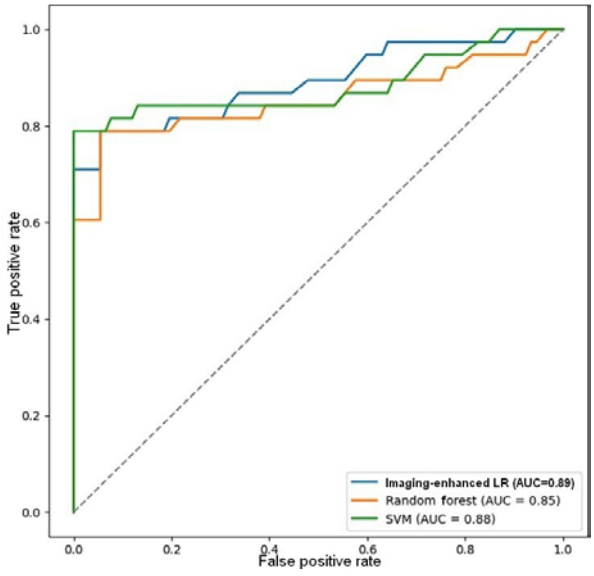

Fig. 3 – Comparison of receiver operating characteristic curves for different predictive models. Dashed lines represent reference lines for random classification. LR – logistic regression; AUC – area under the curve; SVM – support vector machine.

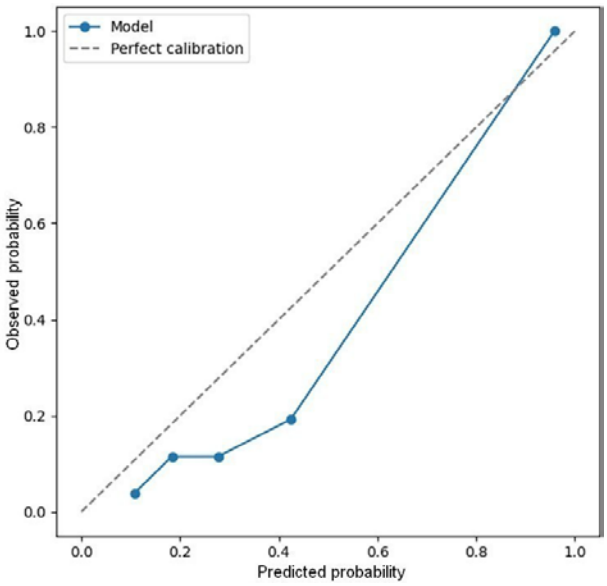

Fig. 4 – Calibration curve of the imaging-enhanced logistic regression model. The dashed line represents the ideal calibration line.

Decision curve analysis of the imaging-enhanced logistic regression model for predicting posterior tibial tendon entrapment

To assess the potential clinical decision-making value of the imaging-enhanced LR model, DCA was further employed to compare its net benefit against "treat-all" and "treat-none" strategies at different threshold probabilities (Figure 5). The results showed that the net benefit of the imaging-enhanced LR model was consistently higher than that of the treat-all and treat-none strategies within the clinically relevant interval of threshold probability of about 0.10–0.50, with a generally stable curve profile. In contrast, the net benefit of the treat-all strategy decreased rapidly as the threshold probability increased, while the treat-none strategy yielded a constant net benefit of zero across all threshold intervals. These findings suggest that, within a reasonable preoperative risk threshold range, preoperative risk assessment and intraoperative exploration decisions based on the imaging-enhanced LR model offer a higher potential net clinical benefit than empirical exploration or no exploration in all patients.

Interpretability analysis of the imaging-enhanced logistic regression model for predicting posterior tibial tendon entrapment

To further elucidate the predictive basis of the imaging-enhanced LR model, the standardized regression coefficients and corresponding ORs of variables in the model were analyzed (Figure 6). The results revealed that imaging structural features dominated the model predictions. CT showed that PTT sheath involvement contributed most significantly to predicting PTT entrapment, with a standardized regression coefficient of 1.98 and an OR of 7.22, suggesting that the risk of tendon entrapment increases significantly when the fracture line extends into the PTT sheath. Posterior AF involvement and more fracture fragments were also significant positive predictors, with a regression coefficient of 0.92 and an OR of 2.52, indicating that fracture complexity and posterior ankle anatomical changes are closely related to tendon entrapment risk. In contrast, age (OR = 0.30) and osteoporosis status (OR = 0.56) exhibited negative or weaker predictive effects in the model, primarily serving as adjustment variables to control for baseline individual differences. Their contribution to the overall predictive power of the model was relatively limited. These results indicate that the predictive performance of the imaging-enhanced LR model primarily derives from anatomical and structural features captured by preoperative imaging, rather than relying solely on individual demographic factors, thereby enhancing the model's interpretability and reliability in clinical application.

Risk stratification analysis of posterior tibial tendon entrapment based on the imaging-enhanced logistic regression model

The actual incidence rate of PTT entrapment showed a clear stepwise distribution across risk groups (Figure 7). In the low-risk group, 49 patients were included, of whom 4 developed PTT entrapment, yielding an incidence rate of 8.2%. The medium-risk group also included 49 patients, 7 (14.3%) of whom had entrapment. In contrast, 32 patients were included in the high-risk group, of whom 27 had intraoperatively confirmed PTT entrapment, with an incidence rate of 84.4%. The incidence rate of PTT entrapment increased significantly with the increase of risk stratification level, suggesting that the model possesses good discriminatory power at the risk stratification level. The above results demonstrate that the imaging-enhanced LR model can not only effectively distinguish patients with different risk levels but also clearly identify high-risk groups, providing a basis for formulating preoperative targeted intraoperative exploration and management strategies.

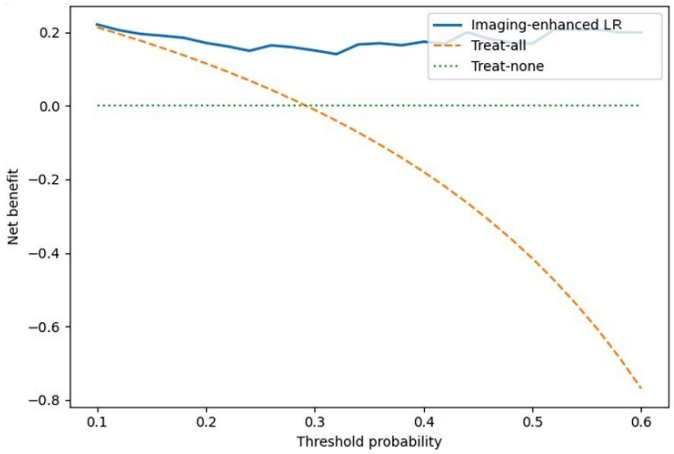

Fig. 5 – Decision curve analysis of the imaging-enhanced logistic regression (LR) model. The net benefit of the imaging-enhanced LR model (solid line) at different threshold probabilities is shown and compared with treat-all (dashed line) and treat-none (dotted line) strategies.

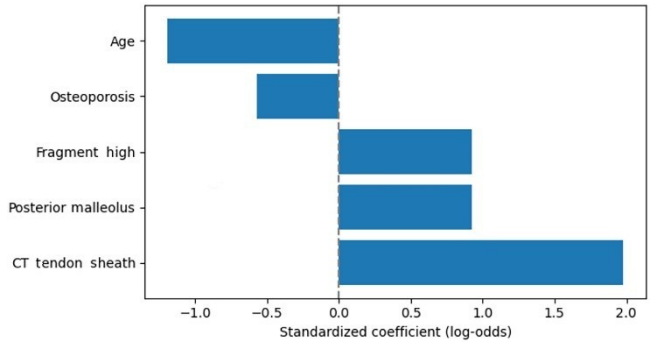

Fig. 6 – Standardized regression coefficients for variables in the imaging-enhanced logistic regression model. The bar chart displays standardized regression coefficients (log-odds) for predictor variables in the model, with positive values indicating an increased risk and negative values indicating a decreased risk. CT – computed tomography.

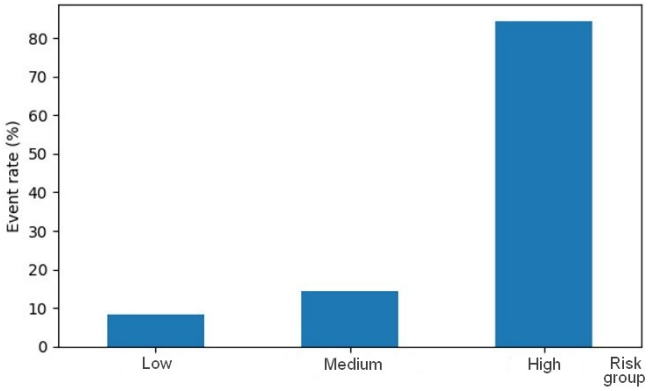

Fig. 7 – Actual incidence rate of posterior tibial tendon entrapment across different risk stratification levels.

Intraoperative grading processing results of posterior tibial tendon entrapment based on preoperative risk stratification

Further analysis of the correlation between preoperative risk stratification and intraoperative entrapment grading showed that patients predicted as low risk preoperatively were more likely to correspond to grades 0–1, and they underwent relatively simple intraoperative management. Medium-risk patients were mainly concentrated in grades 1–2. The proportion of grades 2–3 entrapment was significantly higher in high-risk patients. This denotes that as the preoperative pre-

dicted risk rises, both the intraoperative entrapment grade and the complexity of the procedure correspondingly increase.

Discussion

This study developed and validated an imaging-enhanced predictive model based on preoperative available clinical and imaging data of elderly patients with AFs, enabling preoperative identification of high-risk individuals for PTT entrapment. The results showed that PTT entrapment occurred with a certain frequency (29.2%) in the elderly with AFs, and it was closely associated with the fracture morphology and local anatomical structure changes reflected by preoperative CT. Incorporating imaging structural features significantly enhanced the predictive model's discriminatory power, enabling effective preoperative risk stratification. This provides a reference for determining whether targeted exploration and corresponding management should be performed intraoperatively.

In this study, 29.2% of the elderly patients with AFs were confirmed to have PTT entrapment intraoperatively, indicating a relatively high incidence rate of this complication in this population. The previous report on PTT entrapment has primarily focused on case reports or small-sample retrospective analyses, often treating it as an incidental intraoperative problem, lacking a systematic understanding of its occurrence characteristics [16]. The results of this study suggested that PTT entrapment was common in elderly patients with AFs and that relying solely on routine intraoperative experience may carry a risk of missed diagnosis. Considering the important role of PTT in maintaining medial stability of the ankle joint and arch function, failure to promptly identify and address its intraoperative entrapment may increase surgical complexity and adversely affect postoperative functional recovery [17]. Therefore, systematic evaluation of PTT entrapment holds definite clinical significance in the diagnosis and treatment of AFs in the elderly.

This study revealed that PTT entrapment primarily results from local anatomical changes caused by fractures, a process that can be clearly visualized on preoperative CT imaging. Under normal conditions, PTT runs along the posterior margin of the tibia and behind the medial ankle. Its smooth sliding depends on continuous bony structures and a relatively intact tendon sheath environment [18, 19]. When AFs involve the posterior ankle, especially comminuted fractures, the integrity of the posterior tibial margin is disrupted, and the originally smooth sliding interface is replaced by irregular fracture sections or loose bone fragments [20]. During fracture reduction and internal fixation, these changes create potential mechanical entrapment points along the tendon course. If the fracture line further involves the PTT sheath, the surrounding tendon sheath structures and soft tissue barriers become compromised, significantly increasing the likelihood of direct contact between the tendon and fracture fragments [21]. In such cases, even if the overall reduction of the fracture proceeds smoothly, PTT may still be passively embedded in the fracture gap due to local space constraints, resulting in entrapment that is difficult to detect immediately intraoperatively [22]. At the same time, a comminuted fracture is often accompanied by extensive local soft tissue injury and disrupted anatomical relationships. This complex fracture morphology not only increases the probability of PTT entrapment, but also creates conditions for the subsequent formation of soft tissue adhesion [23]. In this study, the intraoperative morphological observation aligned with these hypotheses. Among patients with PTT entrapment, entrapment predominantly occurred within the posterior AF gap, and only about half of the cases showed simple mechanical incarceration. A considerable number of patients had concurrent soft tissue adhesion of varying degrees, and a few cases even had concurrent tendon surface injury. In contrast, demographic factors such as age and sex had relatively limited predictive value in the model and did not directly contribute to the formation of PTT entrapment. Based on the above findings, it can be concluded that the occurrence of PTT entrapment is mainly related to the change in fracture morphology and local anatomical relationship, and its risk mainly depends on the relationship between bone and soft tissue shown by preoperative imaging, which mechanistically supports the rationale for systematic assessment using preoperative CT scans.

Based on the close relationships of PTT entrapment with fracture morphology and local anatomical changes, this study incorporated relevant imaging features into the predictive model and further evaluated their value in preoperative risk identification and clinical decision-making. The results showed that incorporating imaging data such as the number of fracture fragments and PTT sheath involvement significantly enhanced the model's discriminatory and risk stratification capabilities (AUC 0.72 vs. 0.89). This improvement was reflected not only in the enhancement of overall discriminatory power but also in the identification of high-risk patients. Following risk stratification based on the model's predicted probabilities, the actual incidence of PTT entrapment demonstrated a distinct gradient across risk tiers, with the high-risk group exhibiting a significantly higher rate of intraoperatively confirmed entrapment. The results suggest that the imaging-enhanced model not only statistically improves predictive performance but also distinguishes patients with a genuine risk of PTT entrapment preoperatively, making the predictive results closer to the real surgical scenarios. Furthermore, DCA showed that preoperative assessment based on the imaging-enhanced model resulted in higher net benefit and better decision performance than routine exploration or no exploration for all patients within clinically common threshold probabilities. These findings demonstrate that incorporating imaging structural features not only significantly enhances the discriminatory power of the model but also increases its practical value in preoperative risk stratification and intraoperative decision support.

Some limitations are worth noting in this study. Firstly, as a single-center retrospective study with a relatively

limited sample size, further validation of the model's robustness and external applicability through multicenter studies is required. Secondly, intraoperative morphologic assessment and management strategies depend to some extent on surgeon experience, potentially introducing observer variability. Future studies incorporating a prospective design can be conducted to validate the imaging predictive results across different surgeons and clinical settings, thereby further improving the preoperative assessment and intraoperative management process of PTT entrapment.

Conclusion

In conclusion, posterior tibial tendon entrapment occurs with a certain frequency in elderly patients with ankle fractures, warranting clear clinical attention. Based on fracture morphology and local anatomical structure reflected by preoperative computed tomography, a relatively reliable preoperative assessment of posterior tibial tendon entrapment risk can be performed. Compared with prediction methods that rely solely on basic clinical characteristics, predictive models incorporating imaging features significantly improve risk identification and effectively stratify high-risk patients preoperatively. Combined with intraoperative morphological validation results, the imaging-enhanced model has potential clinical value in guiding preoperative evaluation and optimizing intraoperative management strategies.

Conflict of interest

The authors declare no conflict of interest.

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Impact of prosthodontic rehabilitation on oral health-related quality of life in the Serbian Armed Forces personnel

Uticaj protetske rehabilitacije na kvalitet života povezan sa oralnim zdravljem pripadnika Vojske Srbije

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Abstract

Background/Aim. Although prosthodontic rehabilitation restores the structural integrity of the stomatognathic system, its impact on patients' oral health–related quality of life (OHRQoL) remains insufficiently explored, particularly within the military population. The aim of this study was to evaluate the association between the type of prosthetic rehabilitation and OHRQoL, with a specific focus on functional, esthetic, and psychosocial dimensions, as well as to investigate the relationship between these findings and objective oral health indicators. **Methods.** A cross-sectional study was conducted to assess patient-reported outcomes using the Oral Health Impact Profile-14 (OHIP-14) questionnaire. The study included active duty personnel of the Serbian Armed Forces with natural dentition, as well as personnel with fixed or removable prostheses. Dental status was evaluated through comprehensive clinical examinations conducted by two experienced examiners. Biological parameters included the Caries Activity Factor (CAF) index, the Community Periodontal Index of Treatment Needs (CPITN), the plaque index (PI), and the gingival index (GI). Chronic systemic disease was recorded and included as a covariate in the analyses. Nonparametric statistical tests and multivariable regression analyses were employed to identify independent predictors of OHRQoL. **Results.** Participants with prostheses reported significantly higher OHIP-14 scores than those with natural dentition ($p < 0.0001$). No significant differences were observed between fixed and removable prostheses in overall OHIP-14 scores, except within the functional limitation domain, in which fixed prostheses demonstrated a measurable advantage. Multivariable analysis identified oral status, CAF and CPITN indices, and the presence of chronic systemic diseases as independent predictors of OHRQoL, whereas PI, GI, and age were not statistically significant after adjustment. **Conclusion.** According to the results of this study, prosthetic rehabilitation is associated with improved functional outcomes, but it did not fully alleviate the psychosocial burden associated with tooth loss. The severity of biological oral diseases and general health status were significant predictors of OHRQoL, suggesting that these factors may influence overall quality of life.

Keywords:
dental prosthesis; military personnel; oral health; quality of life; serbia; surveys and questionnaires.

Apstrakt

Uvod/Cilj. Mada se protetskom rehabilitacijom obnavlja strukturni integritet stomatognatog sistema, njen uticaj na kvalitet života povezan sa oralnim zdravljem (*health–related quality of life* – OHRQoL) pacijenata još uvek nije dovoljno ispitan, posebno u vojnoj populaciji. Cilj rada bio je da se proceni povezanost između tipa protetske rehabilitacije i OHRQoL, sa posebnim naglaskom na funkcionalne, esteteske i psihosocijalne dimenzije, kao i da se ispita odnos tih nalaza sa objektivnim pokazateljima oralnog zdravlja. **Metode.** Sprovedena je studija preseka kako bi se procenili ishodi koje prijavljuju sami ispitanici korišćenjem upitnika *Oral Health Impact Profile*-14 (OHIP-14). U istraživanje su bili uključeni pripadnici stalnog sastava Vojske Srbije sa prirodnom denticijom, kao i pripadnici sa prisustvom fiksnih ili mobilnih zubnih nadoknada. Status zuba je procenjivan kroz sveobuhvatne kliničke preglede koje su sprovodila dva iskusna ispitivača. Biološki parametri obuhvatili su indeks

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aktivnosti karijesa (*Caries Activity Factor* – CAF), parodontalni indeks potreba za tretmanom (*Community Periodontal Index of Treatment Needs* – CPITN), plak indeks (*plaque index* – PI) i gingivalni indeks (GI). Hronična sistemska bolest je zabeležena i uključena kao kovarijata u analizama. Neparametrijski statistički testovi i multivarijantna regresiona analiza korišćeni su za identifikaciju nezavisnih prediktora OHRQoL. **Rezultati.** Učesnici sa zubnim nadoknadama imali su značajno više skorove upitnika OHIP-14 od učesnika sa prirodnim zubima ($p < 0{,}0001$). Nisu primećene značajne razlike između fiksnih i mobilnih zubnih nadoknada u ukupnim rezultatima na OHIP-14 skali, osim u domenu funkcionalnih ograničenja, u kom je pokazana merljiva prednost fiksnih nadoknada. Multivarijabilnom analizom kao nezavisni prediktori OHRQoL identifikovani su oralni status, indeksi CAF i CPITN, kao i prisustvo hroničnih sistemskih oboljenja, dok PI, GI i starost nisu pokazali statističku značajnost nakon prilagođavanja modela. **Zaključak.** Prema rezultatima ovog istraživanja, protetska rehabilitacija je povezana sa boljim funkcionalnim ishodima, ali nije u potpunosti umanjila psihosocijalno opterećenje povezano sa gubitkom zuba. Težina bioloških oralnih oboljenja i opšte zdravstveno stanje bili su značajni prediktori OHRQoL, što ukazuje na to da ti faktori mogu uticati na ukupni kvalitet života.

Ključne reči:
zubna proteza; vojni kolektiv; usta, zdravlje; kvalitet života; srbija; ankete i upitnici.

Introduction

Oral health (OH) is a fundamental component of general health and overall well-being, significantly influencing nutrition, communication, and social interaction. Despite being largely preventable, oral diseases remain among the most prevalent noncommunicable conditions worldwide, affecting approximately 3.5 billion people, nearly half of the global population [1]. Untreated dental caries in permanent teeth represents the most common health condition globally, affecting approximately 2.5 billion individuals, while severe periodontal disease impacts nearly 1 billion people, and complete tooth loss has been reported in approximately 350 million cases [2]. The consequences of poor OH extend beyond physical discomfort, contributing to impaired mastication, speech difficulties, and a reduced quality of life (QoL) [3, 4]. Contemporary dentistry and its specialties offer numerous solutions for the rehabilitation of compromised OH. Among them, prosthodontics plays a particularly important role in maintaining and improving OH by restoring missing teeth and associated structures, rehabilitating impaired masticatory function, and improving esthetics and facial appearance. Given the multidimensional impact of OH conditions and their rehabilitation, understanding the role of prosthodontic treatment in promoting OH is essential for evidence-based clinical practice and the improvement of patient-related outcomes.

Patient-reported outcome measures, such as the Oral Health Impact Profile (OHIP), indicate that nearly 47.5% of the elderly population reports poor oral health–related QoL (OHRQoL), with physical pain and psychological disability being the most affected domains [5]. These findings underscore the importance of incorporating subjective assessments that capture patient perceptions and psychosocial impacts alongside objective clinical evaluations [6]. Subjective measures, including self-reported OH status, functional limitations (FLs), and QoL questionnaires, provide valuable insights into the lived experience of oral conditions and their social consequences [7]. Furthermore, self-reported OHRQoL represents an important indicator of both disease burden and therapeutic outcomes [8]. Conversely, OH, as a critical component of overall well-being, can be objectively assessed using reliable and standardized indices recommended by the World Health Organization (WHO) to evaluate various aspects of dental and periodontal status [9]. Among these, the Caries Activity Factor (CAF) index, the Community Periodontal Index of Treatment Needs (CPITN), the Silness and Löe plaque index (PI), and the gingival index (GI) are widely used tools in both clinical and epidemiological research [10–13].

OHRQoL instruments are inherently culturally sensitive, as they reflect perceptions, values, and social norms that vary across populations and cultural contexts [14]. These tools assess the subjective impact of OH on daily life, which is strongly influenced by cultural expectations related to esthetics, function, and social interaction. When combined with objective OH parameters, they provide a comprehensive framework for assessing OH, guiding clinical decision-making, and supporting OH promotion initiatives. The integration of patient-reported outcomes and objective clinical parameters ensures a holistic approach to identifying risk factors that threaten oral and dental health, while simultaneously raising patient awareness and ultimately improving QoL.

Due to the scarcity of research examining the relationship between OHRQoL and different types of prosthodontic treatments within the military population, the present study was designed to address this gap.

The aim of the study was to evaluate patient-reported functional, esthetic, and psychosocial impacts of prosthodontic restorations on OH and to correlate these findings with objective OH outcomes.

Methods

Study design

The study was designed as a cross-sectional observational investigation and conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [15]. The study was carried out over a 20-month period, from 2016 to 2017.

Ethical approval was obtained from the Institutional Ethics Committee of the Military Medical Academy, Belgrade, Serbia (from May 23, 2012). All study procedures were performed in compliance with the principles of the Declaration of Helsinki for research involving human subjects. Prior to enrollment, all participants were fully informed about the study objectives and data collection procedures and provided written informed consent.

Participants

Participants were recruited from a pool of permanent Serbian Armed Forces (SAF) military personnel of both sexes, in accordance with predefined inclusion and exclusion criteria. Eligible participants were professional SAF members aged 18–64 years who had either complete natural dentition (ND) or fixed prostheses (FPs) or removable prostheses (RPs) in one or both dental arches. Exclusion criteria included civilian SAF employees, acute dental conditions requiring urgent treatment, conditions or therapies that could preclude clinical examination or questionnaire completion, and the use of complete dentures in one or both jaws. Chronic systemic diseases (CSDs) were not an exclusion criterion and were recorded and included as a covariate in the multivariable analyses.

Group analyses

Dental status was evaluated through comprehensive clinical examinations conducted by two calibrated examiners in dental offices located within SAF facilities where officers were stationed. Standard diagnostic instruments, including dental mirrors, probes, artificial lighting, and dental chairs, were used. Based on clinical findings, participants were categorized into three study groups: those wearing FPs in one or both arches (n = 247), those with RPs in one or both arches (n = 31), and those with ND in both arches (n = 1,360).

Biological oral health outcome measures

OH parameters were assessed using standardized indices: CAF, CPITN, PI, and GI. All examinations were conducted under adequate illumination using a mouth mirror and a WHO periodontal probe, where applicable.

The CAF index was evaluated by clinical inspection of all teeth for active lesions, identified by softness, opacity, and plaque retention. Each participant was scored as follows: 0 (no active caries), 1 (one active lesion), or 2 (two or more active lesions). The CAF index was calculated as the sum of individual scores [16].

Periodontal health was assessed using the CPITN system. Dentition was divided into six sextants and examined with a WHO probe (ball tip 0.5 mm). The highest score *per* sextant was recorded as follows: 0 (healthy periodontium), 1 (bleeding on probing), 2 (presence of calculus), 3 (pocket depth 4–5 mm), or 4 (pocket depth ≥ 6 mm). Treatment needs were determined according to CPITN guidelines [17].

Plaque accumulation was measured using PI on six index teeth (16, 12, 24, 36, 32, and 44) [18]. After drying, the gingival third of each tooth was examined and scored as follows: 0 (no plaque), 1 (thin film at the gingival margin), 2 (moderate accumulation within the gingival pocket), and 3 (abundant plaque on the tooth and gingival margin). PI was calculated as the mean of all scores.

Gingival inflammation was assessed using GI on the same index teeth [19]. Color, consistency, and bleeding on probing were evaluated and scored as follows: 0 (normal gingiva), 1 (mild inflammation, slight color change, no bleeding), 2 (moderate inflammation, redness, edema, bleeding on probing), 3 (severe inflammation, marked redness, ulceration, spontaneous bleeding). GI was expressed as the mean score *per* participant.

Patient-reported outcome measures

Patient-reported outcomes were assessed using the OHIP-14 questionnaire [20], adapted for Serbian [21]. The Serbian version of the OHIP-14 has been previously validated by the SAF population [8]. All participants completed OHIP-14 based on their experiences following prosthetic rehabilitation [22]. Questionnaires were administered independently in a quiet and private setting, with clear written and oral instructions, minimizing potential bias and ensuring reliable data collection. OHIP-14 comprises 14 items across seven dimensions: FL, physical pain, psychological discomfort, physical disability, psychological disability, social disability, and handicap. Responses were recorded on a 5-point Likert scale (0 = never, 1 = hardly ever, 2 = occasionally, 3 = fairly often, 4 = very often).

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for macOS, version 31.0 (IBM, Armonk, NY, USA) and GraphPad Prism v.10.4.2.534 (GraphPad Software, San Diego, CA, USA). Normality of continuous variables was assessed using the Shapiro–Wilk test and visual inspection of histograms and quantile-quantile (Q–Q) plots. As OHIP-14 total and domain scores demonstrated non-normal distributions, intergroup comparisons among prosthetic categories were performed using the Kruskal–Wallis test. *Post hoc* pairwise comparisons were conducted using Dunn's multiple comparisons test, with the Holm–Šidák correction applied to control for multiple testing. Multivariable linear regression analyses were performed to identify independent predictors of OHRQoL. The total OHIP-14 score and the FLs domain were analyzed separately as dependent variables. Independent variables included prosthetic status (coded ordinally as ND, FPs, and RPs), age, presence of CSD, CAF, CPITN, PI, and GI indices. All predictors were entered simultaneously using the enter method. Model assumptions were verified through inspection of residual and Q–Q plots. Multicollinearity was assessed using variance inflation factors, all within acceptable limits (< 2.5), indicating model stability. Adjusted R^2 values,

standardized β coefficients, 95% confidence intervals (CI), and *p*-values are reported. A two-tailed *p*-value < 0.05 was considered statistically significant.

Results

Participants

A total of 1,638 participants were included in the study. Males were in the majority [1,456 (88.90%)], compared with females [182 (11.10%)]. The mean age of the overall sample was 33.20 ± 9.60 years. Male participants were significantly older than female participants (33.70 ± 9.60 vs. 27.50 ± 6.60 years; $p < 0.0001$). Participants with ND represented the youngest subgroup (31.77 ± 9.09 years), followed by those with FPs (38.70 ± 9.21 years), whereas participants with RPs constituted the oldest subgroup (42.10 ± 10.13 years), demonstrating a progressive increase in age across prosthetic categories. CSD was reported in 120 (7.30%) participants, while 1,518 (92.70%) participants were systemically healthy. According to oral status, 1,360 participants had ND, 247 had FPs, and 31 had RPs. Participants with CSD were notably older than systemically healthy individuals (41.90 ± 8.00 vs. 32.30 ± 9.30 years).

Oral Health Impact Profile-14

A statistically significant difference in the overall OHIP-14 score was observed among the three groups (ND, FPs, and RPs) (Kruskal–Wallis test: $H = 39.78$, $df = 2$, $p < 0.0001$). *Post hoc* analysis using Dunn's multiple comparisons test with Holm–Šidák correction revealed that patients with FPs had significantly higher OHIP-14 scores compared with those with ND ($p < 0.0001$). Similarly, patients with RPs exhibited significantly higher OHIP-14 scores than participants with ND ($p < 0.0001$). No statistically significant difference was found between the FPs and RPs groups ($p = 0.0892$) (Figure 1A). Significant

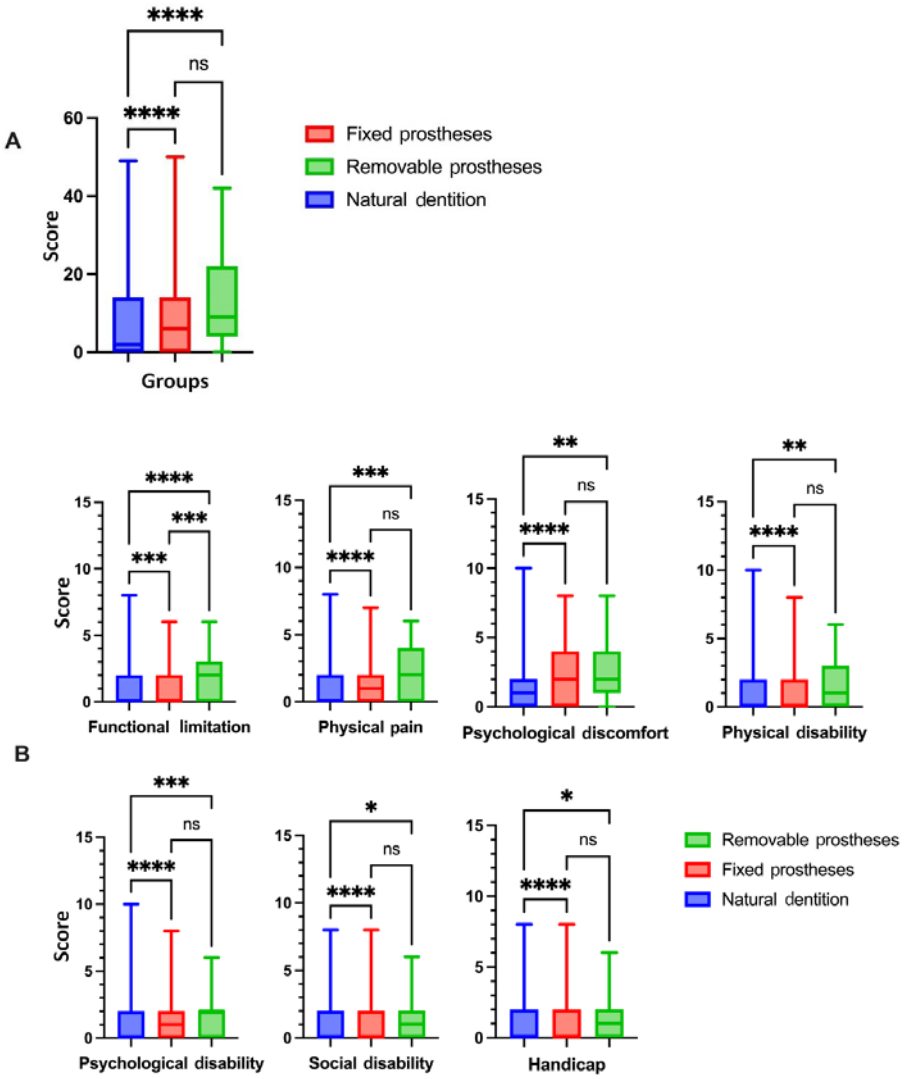

Fig. 1 – Oral Health Impact Profile-14 (OHIP-14) intergroup comparisons: A) total OHIP-14 score; B) OHIP-14 domains (Kruskal–Wallis test; *post-hoc* pairwise comparisons using Dunn's test with Holm–Šidák correction). ns – non-significant;* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$.

differences among the three groups were also observed across all seven OHIP-14 domains (all Kruskal–Wallis tests: $p < 0.0001$), indicating a systematic effect of prosthetic status on OHRQoL. However, the pattern of intergroup differences was domain-specific. Across the majority of domains (physical pain, psychological discomfort, physical disability, psychological disability, social disability, and handicap), *post hoc* analysis consistently showed that both FPs and RPs groups had significantly higher domain scores compared to participants with ND ($p < 0.05$ for all comparisons). No significant differences were detected between the FPs and RPs groups ($p > 0.05$). This suggests that, although FPs improved structural rehabilitation, they did not provide additional psychosocial or handicap-related benefit compared with RPs. In contrast, the FLs domain demonstrated a distinct and clinically relevant gradient, with all three groups differing significantly from one another ($p < 0.001$ for all pairwise comparisons) (Figure 1B). This identifies FLs as the only domain in which fixed prosthetic rehabilitation conferred a statistically significant functional advantage over RPs, whereas RPs were associated with the greatest functional impairment.

Multivariable regression analysis

To further explore determinants of OHRQoL beyond the group-level differences identified by the Kruskal–Wallis and Dunn's *post hoc* tests, a multivariable linear regression model was constructed with the total OHIP-14 score as the dependent variable. Independent predictors included age, oral status, presence of chronic disease, as well as CAF, CPITN, PI, and GI indices (Table 1). The overall regression model was statistically significant ($F = 25.22$, $p < 0.001$) and explained approximately 9.5% of the variance in total OHIP-14 scores (adjusted $R^2 = 0.094$). Oral status remained a statistically significant independent predictor of the total OHIP-14 score (B = 0.996, 95% CI: 0.017–1.974, $p = 0.046$), even after adjustment for age and clinical OH indicators. Oral status was coded as an ordinal variable (1 = ND, 2 = FPs, 3 = RPs), indicating that each incremental worsening in prosthetic category was associated with an approximately one-point increase in OHIP-14 score, reflecting a progressive deterioration in overall OHRQoL, with RPs exerting the greatest negative impact. Additionally, the presence of CSD was associated with significantly higher OHIP-14 scores (B = 1.671, 95% CI: 0.085–3.256, $p = 0.039$), suggesting an independent adverse effect of systemic health on perceived OHRQoL. Biological OH parameters also emerged as strong independent predictors. Each one-unit increase in CAF index was associated with a 0.303-point increase in OHIP-14 score (95% CI: 0.213–0.393, $p < 0.001$), whereas increasing periodontal disease severity (CPITN) corresponded to a 1.069-point increase in OHIP-14 score *per* category (95% CI: 0.214–1.923, $p = 0.014$). Age, PI, and GI were not independently associated with total OHIP-14 scores after adjustment. Collectively, these findings indicate that the overall OHIP-14 score reflects both psychosocial and biological components of OH. Prosthetic status captures a global psychosocial and functional burden perceived by patients, while the CAF and CPITN indices represent objective indicators of clinical oral disease severity, all of which independently contribute to the overall deterioration of QoL.

A separate multivariable regression model was constructed with FLs domain as the dependent variable (Table 2). The model was statistically significant ($F = 20.30$,

Table 1

Multivariable regression analysis – dependent variable OHIP-14 total score

Predictor	B	SE	β	95% CI for B	*p*-value
Oral status, ordinal	0.996	0.499	0.050	0.017–1.974	0.046
Chronic disease, yes	1.671	0.808	0.051	0.085–3.256	0.039
CAF	0.303	0.046	0.171	0.213–0.393	< 0.001
CPITN	1.069	0.436	0.089	0.214–1.923	0.014
PI	0.741	0.576	0.040	- 0.388–1.871	0.198
GI	0.623	0.691	0.033	- 0.733–1.978	0.368
Age, years	0.041	0.027	0.046	- 0.011–0.093	0.121

OHIP-14 – Oral Health Impact Profile-14; SE – standard error; CI – confidence interval; CAF – Caries Activity Factor; CPITN – Community Periodontal Index of Treatment Needs; PI – plaque index; GI – gingival index.
***Note*: Model fit: $R^2 = 0.098$; adjusted $R^2 = 0.094$; F (7,1626) = 25.22.**

Table 2

Multivariable regression analysis – dependent variable functional limitation domain OHIP-14 score

Predictor	B	SE	β	95% CI	*p*-value
Oral status, ordinal	0.135	0.070	0.049	-0.00–0.272	0.054
Chronic disease, yes	0.355	0.113	0.078	0.133–0.577	0.002
CAF	0.027	0.006	0.111	0.015–0.040	< 0.001
CPITN	0.228	0.061	0.138	0.109–0.348	< 0.001
PI	0.093	0.081	0.036	-0.065–0.251	0.249
GI	-0.079	0.097	-0.030	-0.268–0.111	0.416
Age, years	0.007	0.004	0.059	0.000–0.015	0.047

OHIP-14 – Oral Health Impact Profile-14; SE – standard error; CI – confidence interval; CAF – Caries Activity Factor; CPITN – Community Periodontal Index of Treatment Needs; PI – plaque index; GI – gingival index.
***Note*: Model fit: $R^2 = 0.080$; adjusted $R^2 = 0.076$; F (7,1626) = 20.30.**

$p < 0.001$; adjusted $R^2 = 0.076$). Unlike the total OHIP-14 score, oral status was no longer a statistically significant independent predictor of FLs after adjustment for age and clinical OH indicators (B = 0.135, $p = 0.054$). This suggests that the intergroup differences in FLs observed in the Kruskal–Wallis and Dunn's *post hoc* tests were largely attributable to underlying clinical oral disease severity rather than prosthetic status *per se*. Biological factors emerged as the dominant predictors of functional impairment. Each one-unit increase in the CAF index was associated with a 0.027-point increase in FLs score (95% CI: 0.015–0.040, $p < 0.001$), whereas each increment in CPITN corresponded to a 0.228-point increase in FLs score (95% CI: 0.109–0.348, $p < 0.001$). Increasing age was independently associated with worsening FLs (B = 0.007 *per* year, $p = 0.047$), and the presence of CSD further contributed to higher FLs scores (B = 0.355, $p = 0.002$). These findings indicate that FL is predominantly determined by objective biological disease severity and aging, rather than by prosthetic category, explaining why oral status loses independent significance in this domain despite showing big group-level differences in nonparametric analyses.

Discussion

The study evaluated patient-reported outcomes regarding the functional, esthetic, and psychosocial impacts of prosthodontic treatment on OHRQoL using the OHIP-14 questionnaire. In addition, biological OH parameters, including CAF, CPITN, PI, and GI indices, were assessed to evaluate the overall burden of oral disease. The sample was drawn exclusively from SAF personnel, which may limit generalizability to the broader population due to unique occupational and lifestyle factors, differential access to care, and psychosocial influences that differ from civilians. Nevertheless, the study addresses a significant gap in the literature by examining the impact of prosthodontic treatment on OHRQoL in a Serbian military population, a setting where such data are scarce. By focusing on military personnel, a relatively underexplored population, these results contribute novel insights to the scientific literature and help bridge the knowledge gap regarding the comparative effects of different prosthetic restorations on patients' OHRQoL, highlighting the importance of individualized treatment planning in prosthodontic practice [23]. Patient-reported outcomes were assessed using the OHIP-14 questionnaire, providing a comprehensive evaluation of functional, esthetic, and psychosocial impacts of prosthodontic interventions. While self-reported data are inherently subject to recall and social desirability biases, which may influence OHIP-14 responses, the instrument is validated and widely recognized as a rigorous measure of OHRQoL [24, 25].

The study findings suggest that, although prosthetic rehabilitation is associated with restoration of structural integrity, it may not fully mitigate the psychosocial burden associated with tooth loss. Participants with both FPs and RPs reported significantly higher OHIP-14 scores compared with individuals with ND, indicating a persistent negative effect on perceived QoL. Although patient satisfaction and OHRQoL overlap in some areas, patients generally expect that prostheses will primarily improve their overall QoL [26]. These results align with previous research in civilian populations, suggesting that prosthetic treatment may be associated with better functional outcomes, although it cannot entirely replicate the comfort and confidence associated with ND [27, 28]. Interestingly, no significant difference was observed between FPs and RPs in overall OHIP-14 scores, except within FLs domain. This domain displayed a clear gradient, with FPs being associated with a measurable functional advantage over RPs. These findings emphasize the importance of considering functional outcomes separately from psychosocial dimensions when evaluating prosthetic success. Therefore, the influence of prosthodontic treatment on QoL extends beyond mere restoration of oral function [29]. While FPs may enhance mastication and speech, they do not appear to provide additional psychological or social benefits compared with RPs. Similar findings were reported in another study, where patient satisfaction was more closely associated with the psychological than the physical domain of OHIP [30].

Multivariable regression analysis further demonstrated that oral status remained an independent predictor of overall OHRQoL even after adjustment for age and clinical indicators, confirming its role as a global determinant of patient-perceived burden. Similarly, a study using hierarchical multiple regression analysis reported that OH status remained significantly associated with OHRQoL after controlling for demographic and clinical variables, reinforcing its importance as an independent predictor [31]. However, within the FLs domain, oral status lost statistical significance once biological variables were included in the model, suggesting that functional impairment is primarily driven by objective disease severity rather than prosthetic category. This finding highlights the complex interplay between structural rehabilitation and underlying OH conditions.

Biological indicators, specifically CAF and CPITN indices, emerged as strong independent predictors of both overall OHIP-14 and FLs scores. Each incremental increase in these indices was associated with a significant deterioration in QoL, reinforcing the notion that untreated caries and periodontal disease exert a substantial impact beyond clinical symptoms, affecting daily functioning and psychosocial well-being. Although reported in a military population, our findings are consistent with previous reports demonstrating a clear correlation between increasing periodontitis severity and higher OHIP-14 scores, particularly in Stage III and IV disease, indicating marked impairment in QoL [32]. Furthermore, greater caries experience was associated with worse OHIP-14 scores, confirming the detrimental effect of untreated caries on daily functioning and psychosocial well-being [33].

CSD also contributed negatively to OHRQoL, reflecting the multidimensional nature of OH and its interaction with general health. Consistent with these

findings, previous studies have shown that patients with chronic systemic conditions, such as diabetes mellitus, cardiovascular disease, and hypertension, exhibit significantly poorer OH parameters, including a higher prevalence of periodontitis and tooth loss, underscoring the need for integrated and interdisciplinary care approaches [34].

Contrary to expectations, PI, GI, and age were not significant predictors of overall OHIP-14 scores after multivariable adjustment, although both age and the presence of CSD significantly influenced the FLs domain. These findings are consistent with previous studies reporting no direct association between mild-to-moderate plaque accumulation or gingival inflammation and overall OHRQoL [13, 35]. This suggests that while plaque accumulation and gingival inflammation are important targets for clinical management, their direct impact on patient-perceived QoL may be outweighed by more severe conditions, such as active caries lesions and advanced periodontal pockets. Nevertheless, contradictory evidence exists, as some studies have demonstrated that self-reported gingival bleeding is associated with poorer OHRQoL, indicating that patient-perceived symptoms may influence QoL outcomes independently of clinical indices [36].

Collectively, these findings emphasize the necessity for comprehensive treatment strategies that simultaneously address prosthetic rehabilitation and underlying biological disease. Merely replacing missing teeth does not guarantee improvements in psychosocial well-being; effective control of caries activity and periodontal disease is equally essential. Furthermore, FLs should be considered a key outcome measure in prosthetic planning, as it reflects meaningful improvements in patients' functional capacity and daily performance.

A major strength of this study lies in the combined use of nonparametric group comparisons and multivariable regression modeling, which enabled the differentiation of overall group effects from independent biological determinants of OHRQoL. This analytical approach enhances the robustness of the findings by accounting for potential confounding factors while preserving sensitivity to group-level differences.

Limitation of the study

Nevertheless, several limitations should be acknowledged. The cross-sectional study design precludes causal inference; therefore, the observed associations between biological indicators (CAF and CPITN) and OHIP-14 scores cannot be interpreted as causal relationships. It is plausible that pain, discomfort, or functional impairment may lead to poorer oral hygiene practices and reduced dental attendance, rather than biological disease severity alone driving diminished QoL. Furthermore, reliance on the CPITN, based on the worst finding *per* sextant, and the potential use of partial-mouth recording protocols, commonly employed in epidemiological studies, may underestimate the true distribution and severity of periodontal disease compared with full-mouth assessments. This methodological constraint may influence the relative sensitivity of the regression models to GI and PI vs. CPITN. Although the OHIP-14 instrument is widely validated and frequently used in population-based research, its domain-level granularity and responsiveness to clinical change may vary across populations and clinical conditions. In addition, the present study focused exclusively on FPs and RPs, excluding other prevalent treatment modalities such as implant-supported restorations and complete dentures, which may limit the generalizability of the findings. Finally, the cross-sectional nature of the data and reliance on self-reported outcomes introduce the potential for subjective bias and further restrict causal interpretation. Longitudinal studies are therefore warranted to evaluate whether improvements in biological indicators translate into sustained enhancements in OHRQoL following prosthodontic rehabilitation. Complementary qualitative research could also provide deeper insight into patient expectations, perceptions, and satisfaction beyond quantitative QoL scores.

Conclusion

This study suggests that prosthodontic rehabilitation in military personnel, although essential for restoring oral function, may not fully alleviate the psychosocial burden associated with tooth loss. While both fixed and removable prostheses were associated with improved functional outcomes, Serbian Armed Forces participants continued to report lower oral health-related quality of life compared with individuals with natural dentition. Oral health indicators, particularly caries activity and periodontal status, emerged as strong independent predictors of oral health–related quality of life, underscoring the necessity for comprehensive treatment strategies that address underlying biological disease in conjunction with prosthetic rehabilitation. These findings suggest the importance of individualized treatment planning that integrates functional, esthetic, and psychosocial dimensions of care, while prioritizing effective disease control to achieve meaningful and sustained improvements in patient-perceived quality of life.

Conflict of interest

The authors declare no conflict of interest.

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Development and preliminary psychometric evaluation of the Psychological Safety Perception scale: an observational study among community pharmacists

Razvoj i preliminarna psihometrijska procena Skale percepcije psihološke bezbednosti: opservaciona studija među farmaceutima u javnim apotekama

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Abstract

Background/Aim. Measuring psychological safety in the workplace is essential for creating an environment where individuals feel safe expressing themselves, thereby promoting optimal patient care. The aim of the study was to develop a reliable and concise scale with preliminary psychometric properties to measure psychological safety in community pharmacies. **Methods.** After scale development through content and face validity, a cross-sectional study was conducted in which data were collected from 216 community pharmacists. A test-retest component was subsequently performed on 32 pharmacists at baseline and after three months to assess the temporal stability of the scale. Exploratory factor analysis (EFA), confirmatory factor analysis (CFA), the Wilcoxon signed-rank test, and Spearman's correlation coefficient (ϱ) were used to evaluate the scale's reliability, construct validity, and stability. **Results.** The scale was developed through multiple iterations: Version 1 (32 items), Version 2 (26 items), and Version 3 (15 items), all of which demonstrated high content and face validity (indices > 0.80) and internal consistency (Cronbach's alpha = 0.92). Version 4 (10 items) was established through CFA, which suggested excluding certain items, resulting in excellent reliability (Cronbach's alpha = 0.89) and fit parameters: $\chi^2(35) = 65.81$; $p < 0.001$; goodness of fit index – GFI = 0.94; comparative fit index – CFI = 0.97; Tucker-Lewis index – TLI = 0.96; root mean square error of approximation – RMSEA = 0.064; standardized root mean square residual – SRMR = 0.040. During psychometric evaluation, EFA revealed a one-factor structure, with the primary component explaining nearly 50% of the variance. The Wilcoxon signed-rank test indicated no significant difference in mean scores between baseline [mean = 50.72, standard deviation (SD) = 12.93] and retest after three months (mean = 50.69, SD = 12.59). Additionally, Spearman's correlation coefficients showed strong correlations between baseline and three-month scores ($\varrho = 0.994$; $p < 0.001$). **Conclusion.** The findings indicate promising preliminary psychometric properties, supporting the use of the developed scale to assess psychological safety perceptions in community pharmacies. However, further validation, including criterion, convergent, and discriminant validity testing, is required.

Keywords:
data interpretation, statistical; pharmacies; pharmacists; psychological safety; surveys and questionnaires.

Apstrakt

Uvod/Cilj. Merenje psihološke bezbednosti na radnom mestu od ključnog je značaja za stvaranje okruženja u kojem se pojedinci osećaju sigurno da izraze svoje mišljenje, što unapređuje optimalnu negu pacijenata. Cilj rada bio je razvoj pouzdane i sažete skale sa preliminarnim psihometrijskim svojstvima za merenje psihološke bezbednosti u apotekama. **Metode.** Nakon razvoja skale procenom validnosti sadržaja i procenom pojavne (*face*) validnosti, sprovedena je studija preseka u kojoj su prikupljeni podaci od 216 farmaceuta zaposlenih u apotekama. Postupak test-retest je potom sproveden kod 32 farmaceuta na početku ispitivanja i posle tri meseca, da bi se procenila stabilnost skale tokom vremena. Za procenu pouzdanosti, konstruktivne validnosti i stabilnosti, korišćene su eksploratorna faktorska analiza (*exploratory factor analysis* – EFA), konfirmatorna faktorska analiza (*confirmatory factor analysis* – CFA), Wilcoxon-ov test ranga i Spearman-ov koeficijent korelacije (ϱ). **Rezultati.** Skala je razvijana kroz mnogobrojne revizije verzija 1 (32 stavke), verzija 2 (26 stavki) i verzija 3 (15 stavki), pri čemu su sve pokazale visoku validnost sadržaja i pojavnu validnost (indeksi > 0,80) i internu konzistentnost

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(Cronbach-ov koeficijent alfa = 0,92). Verzija 4 (10 stavki) uspostavljena je putem CFA, na osnovu koje je predloženo isključivanje određenih stavki, čime su postignuti odlična pouzdanost (Cronbach-ov koeficijent alfa = 0,89) i parametri uklapanja: $\chi^2(35) = 65,81$; $p < 0,001$; *goodness of fit index* – GFI = 0,94; *comparative fit index* – CFI = 0,97; *Tucker-Lewis index* – TLI = 0,96; *root mean square error of approximation* – RMSEA = 0,064; *standardized root mean squared residual* – SRMR = 0,040. Tokom psihometrijske procene, EFA je pokazala jednofaktorsku strukturu, pri čemu je primarna komponenta objašnjavala skoro 50% varijanse. Wilcoxon-ovim testom rangova nije pokazana značajna razlika između prosečnih rezultata na početku [srednja vrednost = 50,72, standardna devijacija (SD) = 12,93] i posle tri meseca (srednja vrednost = 50,69, SD = 12,59). Pored toga, koeficijentom Spearman-ove korelacije pokazana je jaka povezanost između početnih i tromesečnih rezultata ($\varrho = 0,994$; $p < 0,001$). **Zaključak.** Rezultati ukazuju na obećavajuća preliminarna psihometrijska svojstva, što podržava korišćenje razvijene skale za procenu percepcije psihološke bezbednosti u javnim apotekama. Međutim, neophodna je dodatna validacija, uključujući testiranje kriterijumske, konvergentne i diskriminativne validnosti.

Ključne reči:
statistička analiza podataka; apoteka; farmaceuti; bezbednost, psihološka; ankete i upitnici.

Introduction

Psychological safety (PS) is a state where individuals or groups feel secure, supported [1], and free to express thoughts and feelings without fear of judgment or punishment [2, 3]. It is essential for mental health, productivity, and fostering positive relationships and collaboration within communities [4, 5]. This sense of security and freedom from fear [3] is foundational for individual well-being and productivity [6], and is crucial for building strong, collaborative environments in communities and organizations [3, 6].

PS is vital for organizational success, especially in healthcare teams [1]. It is crucial in the pharmaceutical sector [5], particularly for community pharmacists under high-pressure situations affecting patient care [7, 8]. Integrating interdisciplinary perspectives and innovative methodologies enhances our understanding of PS [1] within this sector. Using mixed-methods approaches, which combine quantitative data with qualitative interviews, researchers gain comprehensive insights into the complex dynamics in community pharmacies [5]. This approach explores how regulatory demands, commercial pressures, and interpersonal relationships impact PS, providing holistic data essential for developing effective interventions tailored to community pharmacists' unique challenges [5].

While team-level surveys are common for assessing PS, comprehensive measures are needed in healthcare [1]. Healthcare organizations can use staff surveys [2] and observational frameworks [2, 3], despite concerns about staff burden [4]. Although measuring its direct impact on healthcare outcomes is challenging [2, 3], indicators like the willingness to voice concerns can show progress [3, 4]. Long-term evaluation through surveys and ongoing assessment is crucial for fostering cultural change [2–4]. Developing a reliable scale for PS in complex settings, like pharmacies, is essential for maintaining quality care. Pharmacists' decisions directly affect patient health, so their well-being is vital. A tailored scale can identify factors influencing their sense of safety, enabling targeted interventions to enhance performance and well-being [5]. Existing tools [1, 6, 9] may provide a basic understanding but often lack relevance to the pharmaceutical environment, which faces unique regulatory, ethical, and commercial pressures [9]. These tools are often too lengthy for the fast-paced nature of pharmacy work [10]. A new, concise, and tailored instrument is essential for community pharmacists to accurately capture the nuances of PS within healthcare systems. Transitioning from traditional measurement methods to contemporary approaches underscores the need for specialized instruments with validated structures [9, 10]. This will enable practical integration into daily operations, providing a robust framework for evaluation across various teams and departments [10].

The aim of this study was to create a concise self-report scale for measuring PS among community pharmacists, designed for easy administration in a fast-paced environment. Unlike traditional metrics, this scale captures pharmacists' nuanced experiences, providing a comprehensive understanding of PS in community pharmacies. It serves both research and organizational assessment purposes, enhancing understanding and management of PS.

Methods

This observational study employed a cross-sectional design with a three-month test-retest component to assess the temporal stability of the instrument. The initial survey was used for psychometric evaluation of the PS scale. STROBE (Strengthening the Reporting of Observational studies in Epidemiology) checklist [11] documents the cross-sectional aspects, particularly in the scale development and psychometric evaluation phase (Supplementary Table 1).

The research spanned from December 2022 to July 2023, encompassing three distinct phases (Figure 1). The time gap between data collection and publication reflects the multi-stage nature of psychometric scale development, including iterative analyses, factor analytic procedures, and manuscript refinement to ensure methodological rigor of the final instrument.

Scale development phase

The development of the PS scale for community pharmacists was a detailed process based on Amy

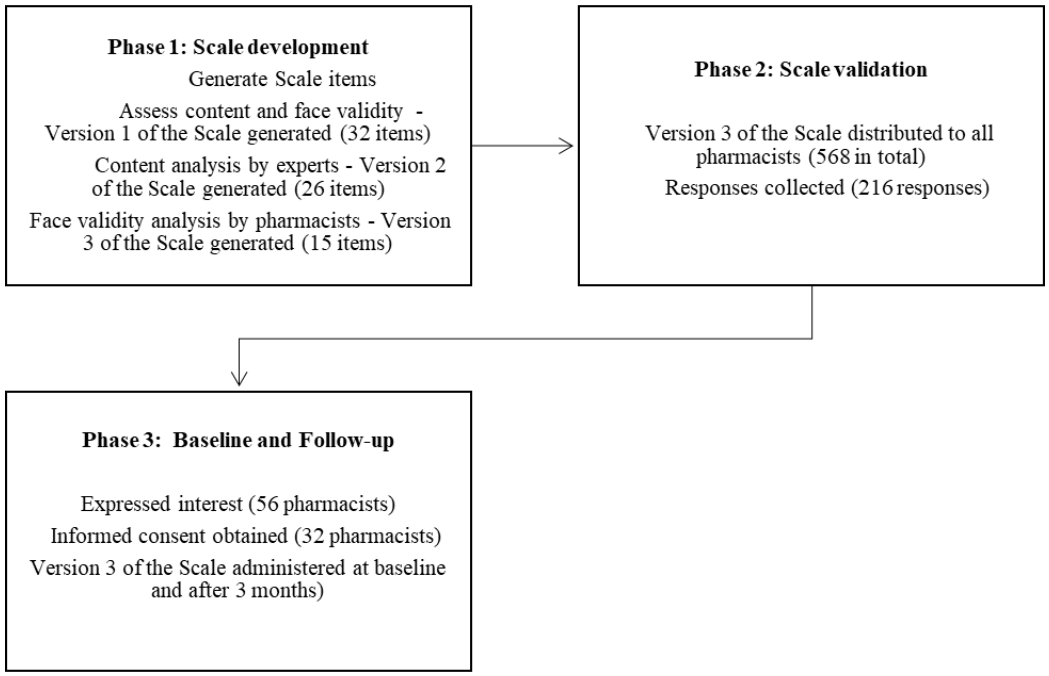

Fig. 1 – Overview of research phases and development process of the Psychological Safety Perception scale.

Edmondson's framework, which emphasizes an environment where individuals feel safe to take interpersonal risks, express ideas, ask questions, voice concerns [12], and admit mistakes without fear of repercussions [13]. Items were selected for their relevance to key theoretical constructs and empirical evidence, and were tailored to daily challenges faced by pharmacists.

To validate content, a panel of six experts (two psychologists, two pharmacists, one psychometric expert, and one faculty professor) was assembled. Experts, selected based on at least 10 years of experience and prior involvement in developing psychological measures, used a 4-point scale to rate each item's relevance. The Content Validity Index (CVI) was calculated, with an Item-Level CVI below 0.80 resulting in item rejection [14].

Face validity was assessed using the Item-Level Face Validity Index (I-FVI), where ten pharmacists with at least 5 years of experience rated each item's clarity on a 4-point scale. Pharmacists with this level of experience were selected to ensure a deeper understanding of the scale's constructs, as less experienced pharmacists might lack this insight. Items with an I-FVI below 0.80 were revised or removed [15], ensuring that only clear and relevant items remained, thereby improving the scale's reliability and practicality. Pilot testing involved ten community pharmacists who completed the initial scale. Feedback from structured interviews and surveys improved item clarity, response format, and instructions, ensuring the scale effectively measures PS. The original surveys were conducted in Serbian, and the questionnaire was translated into English by a bilingual expert using a back-translation method to maintain clarity for English-speaking participants. This preserved the instrument's accuracy, and its validity and reliability in both languages were assessed through pre-testing to enhance applicability in diverse settings. The scale evolved from Version 1 to Version 3 through validation phases, including a cross-sectional study and re-administration at baseline and after 3 months. At the time of data collection, Version 3 was considered reliable and valid for the study. Confirmatory factor analysis (CFA), described later in the text, suggested removing certain items to improve model fit, resulting in Version 4 with ten items, enhancing the scale's psychometric properties and practicality for measuring PS among community pharmacists.

Psychometric evaluation phase

In the psychometric evaluation phase, Version 3 of the Psychological Safety Perception (PSP) scale was used, a 5-point Likert scale with 15 items across five domains: leadership support, trust/respect, organizational/structural support, team support, and interpersonal risk-taking.

Reverse-coded items were omitted for clarity. Respondents rated their agreement from 1 to 5, categorized into low, moderate, and high perceptions based on empirical evidence and theoretical considerations. Cut-off points for these categories were determined from normative data and percentile ranks, supporting nuanced analysis [1, 10]. A questionnaire was electronically administered alongside the scale to gather socio-demographic data, including gender, marital status, age, work experience, education level, and job title. This approach efficiently reached a broader sample of community pharmacists dispersed geographically. Leveraging a secure online platform, measures like automatic checks for incomplete responses and validation rules were employed to ensure data accuracy. Encryption and restricted access protocols were also implemented to maintain confidentiality. To enhance data quality and reduce the risk of careless or random responding, the questionnaire included mandatory item completion, and participants were

required to respond sequentially to all items before submission, preventing skipping of questions.

All pharmacists in the active employee database were invited to participate in the study *via* an electronically distributed scale accessible for 2 months. By completing the scale, pharmacists electronically consented to participate. Active employees were then approached again with a clear explanation of the study's purpose. Interested individuals provided their contact information for further discussions and to sign informed consent forms. Special attention was given to practical considerations, ensuring ease of use and high response rates without disrupting daily operations. The scale aligns with the specific challenges and pressures of pharmacy work, making it a valuable tool for both research and practical application. No financial incentives were offered. Instead, the study's importance for enhancing corporate culture was emphasized.

Baseline and follow-up phase

The study assessed the scale's temporal stability and measurement consistency by administering it twice: at baseline and 3 months later. This procedure was crucial for evaluating the test-retest reliability of the scale, ensuring it consistently measures PS over time. The same participants completed the scale under similar conditions in both sessions to control external variables. This approach verified the scale's reliability in capturing both stable traits and temporary states of PS, ensuring that observed changes reflected actual variations rather than measurement errors or external influences. All participants who entered the test-retest phase completed both measurement points, with no dropouts or refusals reported between baseline and follow-up.

As a result of the psychometric evaluation phase and the baseline and follow-up phase, Version 4 of the scale was developed.

Sample size determination and participants

A priori power analysis was conducted using G*Power (version 3.1.9.4) to determine the minimum required sample size for the Wilcoxon signed-rank test. The analysis assumed an effect size of 0.50, an alpha level of 0.05, and a statistical power of 0.80. The results indicated that a minimum of 21 participants was required. A *post hoc* analysis based on the achieved sample size (n = 32) demonstrated an actual statistical power of 0.85, confirming adequate sensitivity of the study to detect meaningful effects.

Participants for the cross-sectional study were recruited strategically through collaborations with community pharmacies and utilizing the database of all active employees, ensuring variability in the sample. Eligibility criteria included being licensed pharmacists employed in community pharmacies who voluntarily agreed to participate. Measures were implemented to minimize attrition, including regular communication and automated reminders. Ethical rigor was maintained through clear informed consent procedures, including pre-consent sessions and confidentiality measures. The research was conducted within a large healthcare institution comprising 400 community pharmacies distributed across 16 areas, encompassing both urban and rural settings nationwide.

The data essential for contextualizing the research findings and understanding the representativeness of the sample are shown in Supplementary Table 2.

Statistical analysis

For assessing internal consistency and reliability, the Cronbach's alpha coefficient was calculated. In reliability analysis, Cronbach's alpha values above 0.7 are typically acceptable for basic research, while values of 0.8 or higher are preferred for clinical or decision-making contexts [16]. To mitigate potential biases and enhance scale reliability, thorough item analysis and pilot testing were conducted to refine the measurement tool. Additionally, the use of systematic recruitment procedures ensured a broad representation of the target demographic, reducing the risk of selection bias. No missing data was observed for any variable of interest as the questionnaire required mandatory responses, preventing respondents from proceeding to the next question without providing an answer to the preceding one. Although non-parametric tests were applied for inferential analysis, descriptive statistics are reported as mean (M) and standard deviation (SD) to maintain consistency with previous psychometric validation studies [3] and to facilitate comparability of results. Potential confounding variables include years of work experience, level of education, marital status, and job position expressed in type of work.

The distribution of PS scores was evaluated for normality using two tests: Kolmogorov-Smirnov and Shapiro-Wilk. Both tests indicated statistically significant deviations from normal distribution ($p < 0.05$), which justified the use of non-parametric statistical methods. Additionally, due to the non-normal distribution of data resulting from the nature of the PS phenomenon, statistical methods such as the Wilcoxon signed-rank test and Spearman's correlation test were employed. Exploratory factor analysis (EFA) was conducted to identify factor structure based on observed data patterns. To confirm and validate the identified factor structure, CFA was used. Version 3 was subjected to CFA to assess its fit, determining whether it required modification and whether the transition to Version 4 was warranted.

Data analysis was performed using IBM SPSS 29.0.1 at a 95% confidence level. The factor structure of the scale was tested using CFA in IBM SPSS AMOS 22.0.

Ethical approval

Ethical approval was obtained from institutional review boards, ensuring compliance with ethical guidelines and prioritizing participant welfare. This clearance was granted by the Ethics Committee of the Healthcare Institution, as

indicated by decision No. 12/2022 of the Pharmacy Institution Ethics Committee (from December, 2022).

Results

In the second phase, 216 (38%) out of 568 pharmacists responded to the survey, reflecting effective engagement and the study's relevance. However, in the third phase, the response rate dropped to 9.9%, with only 32 pharmacists completing the scale at both baseline and after 3 months, resulting in a final participation rate of 5.6%. The decline was likely due to the long-term follow-up commitment and a lack of financial incentives. Additionally, 57% of the participants who responded to the survey cited time constraints as a concern. The decreasing participation rates underscore the challenges of engaging community pharmacists in research, which are likely due to factors such as workload, time constraints, or a perceived lack of value in participating. While a low participation rate may limit the generalizability of the findings, the study still provides valuable insights by employing rigorous methodological procedures. These results offer a meaningful understanding of PS among those who participated, ensuring that the data collected remains relevant despite the reduced sample size.

Sample 1 consisted of 216 pharmacists aged 20–69 years (M = 39.35, SD = 10.05), with service ranging from 0.5 to 38 years (M = 13.78, SD = 9.56). Sample 2 involved 32 pharmacists aged 20–55 years (M = 36.97, SD = 9.35), with service ranging from 0.5 to 32 years (M = 11.64, SD = 8.96). A detailed representation of the Sample 1 and Sample 2 is provided in Supplementary Tables 3 and 4.

Scale development

Available literature analysis yielded 32 items (Version 1), categorized into five domains: leadership support, trust/respect, organizational/structural support, team support, and interpersonal risk-taking. Version 1 of the scale, comprising 32 items, underwent content analysis. Items with a CVI below 0.8 were excluded (one item from leadership support, one from trust/respect, two from organizational/structural support, one from team support, and one from interpersonal risk-taking), resulting in Version 2 of the scale, which contained 26 items. Version 2 underwent face validity analysis. Items with a face validity index below 0.8 were excluded (two from leadership support, two from trust/respect, three from organizational/structural support, two from team support, and two from interpersonal risk-taking), leading to the creation of Version 3 of the scale, which comprised 15 items containing one item from leadership support, three from trust/respect, three from organizational/structural support, six from team support, and two from interpersonal risk-taking. Version 3 of the scale demonstrates high internal reliability with a Cronbach's alpha of 0.92.

Through the psychometric evaluation process, Version 4 of the scale was created, demonstrating high internal reliability with a Cronbach's alpha of 0.89, indicating satisfactory internal consistency.

The scale development process progressed through four sequential versions, incorporating item revision and psychometric evaluation procedures (Table 1).

Additional details are shown in Supplementary Tables 5 and 6. Both the socio-demographic questionnaire and PSP scale are provided in Serbian and English to ensure transparency, methodological rigor, and international comparability.

Psychometric evaluation

The Kolmogorov-Smirnov test resulted in a statistic of 0.077 with 216 degrees of freedom, leading to a significance level of 0.003. Similarly, the Shapiro-Wilk test produced a statistic of 0.983 with 216 degrees of freedom, yielding a significance level of 0.010. Both Kolmogorov-Smirnov and Shapiro-Wilk tests revealed statistically significant deviations from a normal distribution in PS scores ($p < 0.05$), indicating non-normality of the data and supporting the use of non-parametric statistical methods. Although the data were not normally distributed, descriptive statistics are presented as M and SD to ensure comparability with previously published psychometric studies [3], while inferential analyses were conducted using non-parametric tests [11]. EFA of the 15-item scale revealed the underlying factor structure of PS in community pharmacies, with high communalities (> 0.5) indicating strong item representation. A loading cut-off of 0.40 was applied, and items were retained if their primary loadings exceeded secondary loadings by at least 0.20. The high communalities confirm strong item-factor associations, supporting the observed factor structure of the scale. These results were interpreted in conjunction with CFA to determine the most appropriate factor solution. The first component explains nearly 50% of the total variance, while subsequent components explain less, suggesting the critical importance of the first component in understanding the data structure (Table 2). Rotation of the components did

Table 1

Evolution of Psychological Safety Perception (PSP) scale items – Versions 1 to 4

Domains	PSP scale			
	Version 1	Version 2	Version 3	Version 4
Leadership support	4	3	1	1
Trust/respect	6	5	3	3
Organizational/structural support	8	6	3	2
Team support	9	8	6	3
Interpersonal risk-taking	5	4	2	1
Total number of items	32	26	15	10

Note: **Numbers represent the total number of items included in each version of the scale for the corresponding domain. Version 4 represents the final refined 10-item scale derived from psychometric evaluation.**

not significantly change this relationship, suggesting that the first component could be used as the primary indicator, while the contribution of other components is less pronounced and should be interpreted with caution.

Principal component analysis was utilized as a statistical technique to identify patterns in data and reduce its dimensionality. Using the Varimax method with Kaiser normalization in principal component analysis and rotation, each original variable demonstrated distinct associations with the derived components. Variable 1 displayed a strong association with the first component (coefficient: 0.740), moderate with the second (0.608), and weak with the third (0.287). Variable 2 was notably associated with the third component (0.873), and less so with the first and second components (0.060 and -0.485, respectively). Variable 3 was significantly associated with the second component (0.628), and less so with the first and third components (-0.670 and 0.395, respectively).

First CFA analysis, conducted on Version 3 of the instrument with 15 items, yielded average to poor fit indices: $\chi^2(90) = 351.74$; $p < 0.001$; goodness of fit index (GFI) = 0.82; comparative fit index (CFI) = 0.86; Tucker-Lewis index (TLI) = 0.84; root mean square error of approximation (RMSEA) = 0.116; standardized root mean square residual (SRMR) = 0.067. Based on the analysis of the standardized residual covariances and modification indices from the first CFA, an additional five items were excluded from the scale. One item from the organizational/structural support domain, three items from the team support domain, and one item from the interpersonal risk-taking domain were excluded. The second CFA, conducted on the 10-item scale, exhibited excellent fit parameters: $\chi^2(35) = 65.81$; $p < 0.001$; GFI = 0.94; CFI = 0.97; TLI = 0.96; RMSEA = 0.064; SRMR = 0.040, indicating an improved model fit after item refinement. These adjustments make it clearer that the decision to exclude items was based on the analysis of residual covariances and modification indices from the first CFA. Additionally, it separates the descriptions of the two CFAs for better readability. In this manner, the final Version 4 of the scale with 10 items was obtained. Item loadings are presented, indicating their relative contribution to the latent construct within the proposed model (Table 3).

Table 2

Variant contribution analysis

Component (EFA solution, 15-item scale)	Initial eigenvalues			Rotation sums of squared loadings			
	total	% of variance	cumulative %	total	% of variance	total	% of variance
1	7.491	49.938	49.938	7.491	49.938	4.600	30.666
2	1.277	8.515	58.452	1.277	8.515	3.508	23.384
3	1.102	7.347	65.799	1.102	7.347	1.762	11.750
4	0.879	5.859	71.658				
5	0.690	4.601	76.258				
6	0.556	3.704	79.963				
7	0.526	3.504	83.466				
8	0.467	3.111	86.577				
9	0.391	2.604	89.180				
10	0.364	2.427	91.607				
11	0.324	2.158	93.766				
12	0.303	2.019	95.785				
13	0.250	1.664	97.448				
14	0.205	1.364	98.812				
15	0.178	1.188	100.000				

***Note*: Initial eigenvalues indicate variance explained before rotation. Rotation sums of squared loadings show the variance explained after rotation. Analysis was conducted on a 15-item scale.**
Rotated sums of squared loadings are reported only for the three retained factors, as only these factors were extracted in the final exploratory factor analysis (EFA) solution.

Table 3

Factor loadings

Item	RW (unstandardized)	SE	Critical ratio	*p*-value	RW (standardized)
PS1	0.86	0.072	11.944	< 0.001	0.73
PS2	0.46	0.104	4.385	< 0.001	0.30
PS3	0.85	0.080	10.622	< 0.001	0.67
PS4	0.92	0.068	13.433	< 0.001	0.80
PS5	0.87	0.080	10.923	< 0.001	0.68
PS6	0.47	0.065	7.266	< 0.001	0.49
PS9	0.71	0.070	10.167	< 0.001	0.64
PS10	0.97	0.064	15.182	< 0.001	0.87
PS13	1.00	0.064	14.162	< 0.002	0.82
PS14	0.95	0.071	13.315	< 0.001	0.79

RW – regression weight; SE – standard error; PS – item of the Psychological Safety Perception (PSP) scale, Version 4.

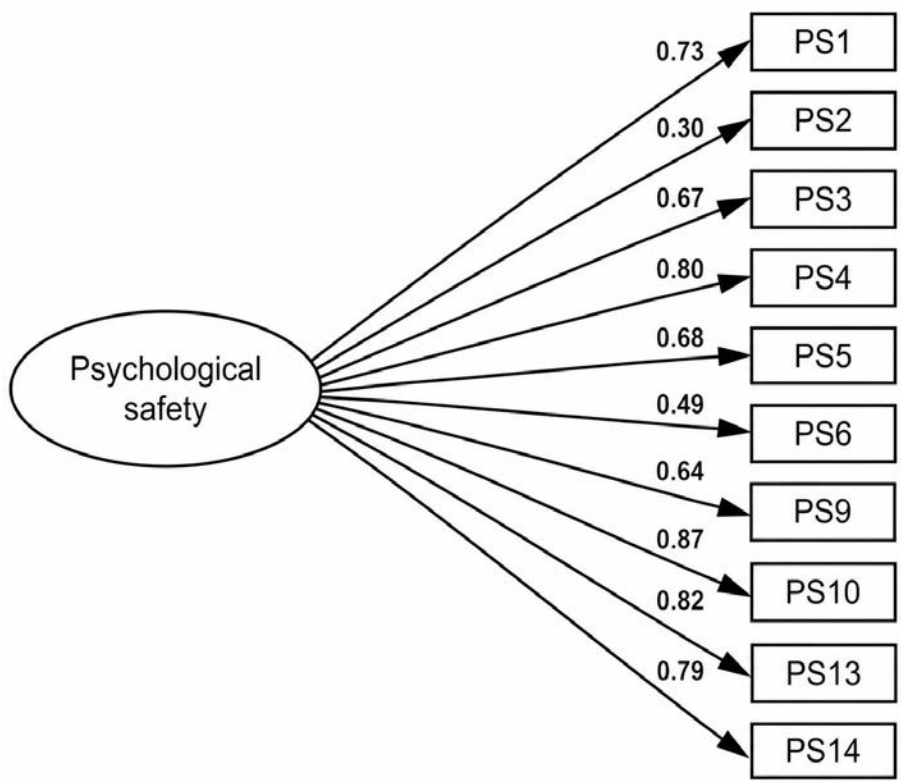

Fig. 2 – Factor loadings.
PS – item of the Psychological Safety Perception scale, Version 4.
***Note*: Factor loadings were obtained using confirmatory factor analysis.**

The relationships between the observed variables and the underlying factors are illustrated, providing a clear depiction of the model's fit and the strength of the associations (Figure 2).

Baseline and follow-up

The Wilcoxon signed-rank test was conducted to compare scores on the PSP scale between baseline and retest, 3 months later, and indicated no statistically significant difference between the two time points (Z = -0.372, p = 0.710), suggesting stability in PS perception over the 3-month period. For the Wilcoxon signed-rank test, an *a priori* power analysis was conducted. The parameters set for this analysis included an effect size of 0.50, a power of 0.80, and an alpha error probability of 0.05. The assumed effect size (r = 0.50) was based on conventional benchmarks for medium effects in behavioral research [17, 18] and on previously reported effect sizes in studies examining PS in healthcare settings [5, 6, 10]. The results indicated that a minimum of 21 participants was required to power the study adequately, given these parameters. The parameters used for the power analysis have been explicitly defined, including effect size, significance level (α), statistical power, and the specific non-parametric test (Wilcoxon signed-rank test) used as the basis for the *a priori* and *post hoc* power calculations, ensuring transparency and reproducibility of the analysis. With 32 participants included in this phase of the study, the sample size was more than sufficient. A *post hoc* analysis of the same group of 32 participants revealed an effective test power of 0.85. This elevated power level, exceeding the initially targeted 0.80, indicates adequate statistical sensitivity of the test. These findings demonstrate that the sample size met the requirements for the planned analyses, supporting the reliability of the statistical testing procedure. Descriptive statistics are reported as M and SD to ensure consistency with established psychometric reporting practices, while inferential analyses were conducted using non-parametric methods due to deviation from normality. Initial PS scores ranged from 24 to 75 (M = 50.72, SD = 12.93), and retest scores after 3 months ranged from 25 to 73 (M = 50.69, SD = 12.59). These consistent scores across testing sessions suggest temporal stability of the measured construct, supporting the test-retest reliability of the developed scale. The PS perception levels remained stable between tests, with 68.8% (n = 22) of participants consistently scoring high, 21.9% (n = 7) moderate, and 9.4% (n = 3) low. Additionally, Spearman's ρ correlation coefficients reveal strong positive correlations between PS score at baseline and after 3 months (ρ = 0.994, p < 0.001), indicating high test-retest consistency and reinforcing the temporal stability of the measurement instrument.

Discussion

The expert review and psychometric evaluation process provides evidence supporting the quality of the concise PSP scale for community pharmacists. Through iterative revisions, content validity was established based on expert feedback, resulting in a streamlined 15-item version. EFA

and CFA support the identification of a predominantly one-factor structure, thus emphasizing teamwork's role, and demonstrate acceptable model fit and internal consistency. CFA further refined the scale into a 10-item version, enhancing its precision. This process provides a preliminary measurement tool for studying PS in community pharmacies. The identified domains–leadership support, trust/respect, organizational/structural support, team support, and interpersonal risk-taking–were used as an initial conceptual framework during item development, but the empirical results suggest that PS may be better represented as a more unified construct in this sample. By assessing pharmacists' perceptions within these areas, organizations can pinpoint gaps or challenges that may impact PS. This targeted approach enables the development of tailored strategies, such as enhancing leadership training, fostering trust-building initiatives, or improving team collaboration, ultimately promoting a healthier work environment and better patient outcomes.

The study emphasizes the importance of reducing item redundancy in PS scales, as supported by prior research. For instance, a study involving 497 employees initially used a 70-item scale, which was refined to a shorter version of 30 items and five factors through factor analysis [3]. This underscores the effectiveness of concise scales for assessing PS in pharmacy settings. Another study focusing on posttraumatic stress disorder confirmed the three-factor structure of the Neuroception of PS scale, demonstrating good validity and reliability with fewer than 30 items. These findings reinforce the value of streamlined scales in accurately evaluating PS [19].

Building on prior research guided by Kahn's definition of PS, which focused on examining PS in the workplace, valuable insights were gained. This study underscored the significance of using a scale with a limited number of items, as it demonstrated that even with only 21 items, a comprehensive assessment of PS can be achieved. Additionally, the study employed CFA to validate the Protect, Support, Encourage, Include – PSEI model, confirming its applicability and robustness in understanding PS dynamics [20]. This research contributes to the broader understanding of PS by emphasizing the effectiveness of a concise measurement approach and providing empirical support in workplace contexts.

Insights from traditional survey methods highlight the need for a practical approach to measure PS effectively. One proposal emphasizes this issue, which is particularly important in healthcare systems where assessment complexities are significant. By devising a composite measure that combines observation and adapted surveys, specifically tailored for healthcare settings, the authors aimed not only to enhance the validity and reliability of measurements but also to provide a more nuanced understanding of PS dynamics within healthcare teams [1]. Additionally, the research by O'Donovan et al. [21] significantly contributes to the existing literature by introducing a systematic approach to developing observational measures that complement traditional survey methods for assessing PS. Their methodology, which incorporates insights from healthcare professionals and aligns with existing PS and healthcare literature, offers a solid foundation for gauging and enhancing PS within healthcare teams [9, 21]. Contemporary research on PS indicates that when measuring, a focused approach is necessary in relation to the setting because numerous factors influence the assessment of PS [22–24]. A focused approach was also confirmed in research with healthcare professionals, highlighting the interaction of numerous variables on the perception of PS, which indicates the importance of selecting precisely those factors that are important for healthcare organizations [25]. The methodological approach applied in this study is consistent with established practices in scale development within pharmacy and healthcare research, where similar psychometric procedures have been widely used [5, 26, 27]. An adequate perception of PS that is consistent with the setting and environment can only lead to cultivating a supportive team culture, thus reinforcing the findings of previous studies [24]. This emphasizes the critical role of teamwork in creating an environment conducive to learning, collaboration, and efficiency [28, 29], which, in the case of healthcare systems, also contributes to the quality of the provided health care [25].

The decision to develop the PSP scale specifically for community pharmacists is supported by the distinctive characteristics of pharmacy practice, which include high levels of patient interaction, time pressure, and interprofessional collaboration within complex healthcare systems. Recent literature highlights that PS is a key determinant of team performance, communication quality, and patient safety in healthcare environments, particularly in settings where professionals operate under high workload demands and frequent decision-making responsibilities [22, 30–32]. In community pharmacy practice, these conditions are especially pronounced, as pharmacists play a critical role in medication safety, patient counseling, and coordination with other healthcare providers [33, 34]. Moreover, recent empirical evidence in pharmacy settings has demonstrated that organizational and behavioral interventions can significantly influence PS perceptions among pharmacists, further emphasizing the relevance of context-specific measurement tools [35, 36]. Accordingly, the development of a pharmacy-specific scale enables more precise assessment of PS within this professional group and contributes to a better understanding of psychosocial dynamics in community pharmacy environments.

Limitations of the study

This study has several limitations that should be acknowledged when interpreting the findings. The gender distribution in the sample, with a predominance of female participants and only one male participant, reflects the actual workforce composition in community pharmacy practice; however, it limits the ability to perform meaningful gender-based comparisons and restricts the generalizability of demographic subgroup analyses. The geographic specificity

of the sample, limited to community pharmacists in Serbia, may restrict the generalizability of the results to other healthcare systems and professional contexts. In addition, the use of self-reported measures may introduce response biases, including social desirability and common method variance.

Although the scale demonstrated satisfactory psychometric properties, several methodological constraints should be considered. Criterion validity was not assessed, as no external measures or outcome variables (e.g., established PS instruments, burnout, or turnover intention) were included. Similarly, convergent and discriminant validity were not examined, limiting conclusions regarding the construct specificity of the scale. As a result, it cannot be ruled out that the scale may partially reflect broader constructs such as general workplace well-being, job satisfaction, or perceived organizational climate rather than PS specifically.

Furthermore, EFA and CFA were conducted on the same sample, which may have inflated model fit indices and limited the confirmatory strength of the findings. Although the scale was theoretically conceptualized as a five-domain instrument, factor-analytic results indicated a unidimensional structure, suggesting that PS may be represented as a global construct in this sample. However, this interpretation requires further validation in independent studies. The relatively small sample size may also limit the stability of parameter estimates and the robustness of factor-analytic results, particularly in the context of CFA conducted on the same sample. Although the sample size was sufficient for the planned analyses based on the *a priori* power calculations, replication in larger and independent samples is recommended to further confirm the stability of the observed factor structure.

This pilot study involved a relatively small sample size, which may limit statistical power and the stability of parameter estimates. In addition, although the 3-month interval for test-retest reliability was selected based on prior research, alternative or longer intervals may provide additional evidence regarding temporal stability.

Conclusion

The scale development process comprised three phases, involving item generation and psychometric evaluation. Expert evaluation and analysis led to the creation of a refined 10-item scale, demonstrating acceptable internal consistency and model fit. Exploratory factor analysis revealed the underlying structure of psychological safety dimensions within the community pharmacy sector, which was confirmed by confirmatory factor analysis. Results indicated that the first component explained a significant portion of variance, highlighting its pivotal role in data interpretation. Additionally, using the Varimax method with Kaiser normalization, distinct associations between original variables and derived components were identified. Furthermore, the Wilcoxon signed-rank test showed no significant difference in psychological safety scores between baseline and retest, affirming stability over 3 months. Importantly, Spearman's ρ correlation coefficients indicated strong positive correlations between psychological safety scores at baseline and after 3 months, indicating consistency in responses.

The study's scale development and repeated measures design offer practical insights for enhancing psychological safety in community pharmacies. The findings underscore the importance of tailored interventions to foster a supportive workplace environment and highlight the critical role of psychological safety in promoting well-being and quality care.

Finally, future research should validate the scale in larger and more diverse samples, including different healthcare settings and professional groups, examine its predictive validity in relation to relevant organizational and patient-related outcomes, and incorporate qualitative methodologies to further refine the understanding of psychological safety in community pharmacy practice. Continued research is essential to strengthen the evidence base and support the development of a psychologically safe pharmacy workforce.

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Supplementary Table 1

STROBE statement – checklist of items that should be included in reports of cross-sectional studies

Items	Recommendation
Title and abstract	a) Indicate the study's design with a commonly used term in the title or the abstract. b) Provide in the abstract an informative and balanced summary of what was done and what was found.
Introduction	
background/rationale	Explain the scientific background and rationale for the investigation being reported.
objectives	State specific objectives, including any prespecified hypotheses.
Methods	
study design	Present key elements of the study design early in the paper.
setting	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection.
participants	a) Give the eligibility criteria, and the sources and methods of selection of participants.
variables	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.
data sources/measurement*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe the comparability of assessment methods if there is more than one group.
bias	Describe any efforts to address potential sources of bias.
study size	Explain how the study size was arrived at.
quantitative variables	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why.
statistical methods	a) Describe all statistical methods, including those used to control for confounding. b) Describe any methods used to examine subgroups and interactions. c) Explain how missing data were addressed. d) If applicable, describe analytical methods taking account of the sampling strategy. e) Describe any sensitivity analyses.
Results	
participants*	a) Report numbers of individuals at each stage of study – e.g., numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed. b) Give reasons for non-participation at each stage. c) Consider the use of a flow diagram.
descriptive data*	a) Give characteristics of study participants (e.g., demographic, clinical, social) and information on exposures and potential confounders. b) Indicate the number of participants with missing data for each variable of interest.
outcome data*	Report the number of outcome events or summary measures.
main results	a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included. b) Report category boundaries when continuous variables were categorized. c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period.
other analyses	Report other analyses done – e.g., analyses of subgroups and interactions, and sensitivity analyses.

Supplementary Table 1 (continued)

Items	Recommendation
Discussion	
key results	Summarize key results with reference to study objectives.
limitations	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both the direction and magnitude of any potential bias.
interpretation	Give a cautious overall interpretation of results, considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.
generalizability	Discuss the generalizability (external validity) of the study results.
Other information	
funding	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based.

STROBE – Strengthening the Reporting of Observational Studies in Epidemiology.
***Note*: *Give information separately for exposed and unexposed groups. An explanation and elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the websites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.**

Supplementary Table 2

Distribution of community pharmacies by area and setting

Pharmacy	Area																
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Total
Urban	16	21	15	17	20	22	15	14	10	15	5	15	13	10	15	7	230
Rural	14	12	10	10	10	8	10	6	15	10	15	10	7	10	10	13	170
Total	30	33	25	27	30	30	25	20	25	25	20	25	20	20	25	20	400

***Note*: Total pharmacies, urban pharmacies, and rural pharmacies are given as the total number of community pharmacies in each area, the number of pharmacies located in urban settings, and the number of pharmacies located in rural settings, respectively.**

Supplementary Table 3

Descriptive statistics of Sample 1 (n = 216) and Sample 2 (n = 32)

Variable	Min–Max	Mean ± SD
Sample 1		
age	20–69	39.35 ± 10.05
years of service	0.5–38	13.78 ± 9.56
psychological safety score	24–75	53.69 ± 11.18
Sample 2		
age	20–55	36.97 ± 9.35
years of service	0.5–32	11.64 ± 8.96
psychological safety test score	24–75	50.72 ± 12.93
psychological safety retest score	25–73	50.69 ± 12.59

n – number; Min – minimum; Max – maximum; SD – standard deviation.

Supplementary Table 4

Demographic characteristics of Sample 1 (n = 216) and Sample 2 (n = 32)

Variable	Sample 1	Sample 2
Gender		
female	204 (94.4)	31 (96.9)
male	10 (4.6)	1 (3.1)
I do not want to make a statement	2 (0.9)	
Marital status		
single	56 (25.9)	10 (31.3)
married	149 (69.0)	20 (62.5)
divorced	9 (4.2)	2 (6.3)
widower/widow	2 (0.9)	

Supplementary Table 4 (continued)

Variable	Sample 1	Sample 2
Degree of professional education		
bachelor	64 (29.6)	12 (37.5)
master	143 (66.2)	18 (56.3)
PhD	9 (4.2)	2 (6.3)
Specialist studies		
yes	22 (10.2)	1 (3.1)
no	194 (89.8)	31 (96.9)
Job position		
pharmacist	127 (58.8)	22 (68.8)
pharmacy manager	89 (41.2)	10 (31.3)
Psychological safety perception level		
low	6 (2.8)	
moderate	47 (21.8)	
high	163 (75.5)	
Psychological safety perception level test		
low		3 (9.4)
moderate		7 (21.9)
high		22 (68.8)
Psychological safety perception level retest		
low		3 (9.4)
moderate		7 (21.9)
high		22 (68.8)

n – number; PhD – Doctor of Philosophy.
Values are presented as numbers (percentages).
***Note*: Blank cells indicate that the variable was not assessed in the respective sample (Sample 1 or Sample 2) as analyses were performed on different subsamples depending on the study phase.**

Supplementary Table 5

All versions of the Psychological Safety Perception (PSP) scale

PSP Version 1

No.	Items	Domains
1	In the team, my abilities and talents are greatly appreciated.	Leadership support
2	My superiors regularly show interest in my opinions and ideas.	Leadership support
3	I feel supported by my leadership when I express concerns or uncertainties.	Leadership support
4	Leaders in my team actively seek feedback from employees to improve the work environment.	Leadership support
5	Seeking assistance from my colleagues is a straightforward process.	Trust/respect
6	I feel empowered to make errors in the workplace without worrying about facing consequences from my colleagues.	Trust/respect
7	None of my colleagues would intentionally behave in a manner that diminishes my contributions.	Trust/respect
8	I trust my colleagues to support me when needed.	Trust/respect
9	I feel respected by my peers and supervisors in the workplace.	Trust/respect
10	There is a high level of mutual trust among team members, which fosters collaboration and open communication.	Trust/respect
11	I am driven to propose innovative ideas to enhance team performance.	Organizational/structural support
12	I am well aware of the requirements of my role in the workplace.	Organizational/structural support
13	My organization provides adequate resources and support for professional development.	Organizational/structural support
14	There are clear channels for reporting concerns or issues within the organization.	Organizational/structural support
15	Organizational policies promote fairness and transparency in decision-making processes.	Organizational/structural support
16	There is effective communication of organizational goals and priorities to all employees.	Organizational/structural support
17	Structural systems within the organization enable efficient workflow and task completion.	Organizational/structural support
18	We have the capability to address challenges and difficult topics in the workplace.	Organizational/structural support

19	The team I am engaged with recognizes and respects my creative capabilities.	Team support
20	My colleagues demonstrate a professional openness to diverse perspectives.	Team support
21	My ideas and suggestions receive support from my colleagues.	Team support
22	My colleagues consistently share relevant work-related information.	Team support
23	My colleagues accept diversity and never exclude others for their differences.	Team support
24	Collaborating with my peers ensures that my distinctive skills and talents are recognized and effectively utilized.	Team support
25	Team members collaborate effectively to achieve common goals.	Team support
26	There is a strong sense of camaraderie and mutual support among team members.	Team support
27	Team meetings provide opportunities for open discussion and problem-solving.	Team support
28	I feel comfortable expressing dissenting opinions or challenging ideas within my team.	Interpersonal risk-taking
29	There is an atmosphere where constructive feedback is encouraged and appreciated.	Interpersonal risk-taking
30	I am confident in sharing my concerns or admitting mistakes without fear of negative consequences.	Interpersonal risk-taking
31	In my professional environment, I feel at liberty to express my authentic self.	Interpersonal risk-taking
32	I feel secure taking work-related risks as they are encouraged in my team.	Interpersonal risk-taking

PSP Version 2

No.	Items	Domains
1	In the team, my abilities and talents are greatly appreciated.	Leadership support
2	I feel supported by my leadership when I express concerns or uncertainties.	Leadership support
3	Leaders in my team actively seek feedback from employees to improve the work environment.	Leadership support
4	I feel respected by my peers and supervisors in the workplace.	Trust/respect
5	There is a high level of mutual trust among team members, which fosters collaboration and open communication.	Trust/respect
6	Seeking assistance from my colleagues is a straightforward process.	Trust/respect
7	None of my colleagues would intentionally behave in a manner that diminishes my contributions.	Trust/respect
8	I feel empowered to make errors in the workplace without worrying about facing consequences from my colleagues.	Trust/respect
9	I am well aware of the requirements of my role in the workplace.	Organizational/structural support
10	We have the capability to address challenges and difficult topics in the workplace.	Organizational/structural support
11	I am driven to propose innovative ideas to enhance team performance.	Organizational/structural support
12	My organization provides adequate resources and support for professional development.	Organizational/structural support
13	There is effective communication of organizational goals and priorities to all employees.	Organizational/structural support
14	Structural systems within the organization enable efficient workflow and task completion.	Organizational/structural support
15	The team I am engaged with recognizes and respects my creative capabilities.	Team support
16	My colleagues demonstrate a professional openness to diverse perspectives.	Team support
17	My ideas and suggestions receive support from my colleagues.	Team support
18	My colleagues consistently share relevant work-related information.	Team support
19	My colleagues accept diversity and never exclude others for their differences.	Team support
20	Collaborating with my peers ensures that my distinctive skills and talents are recognized and effectively utilized.	Team support
21	Team members collaborate effectively to achieve common goals.	Team support
22	Team meetings provide opportunities for open discussion and problem-solving.	Team support
23	I feel comfortable expressing dissenting opinions or challenging ideas within my team.	Interpersonal risk-taking

24	I am confident in sharing my concerns or admitting mistakes without fear of negative consequences.	Interpersonal risk-taking
25	I feel secure taking work-related risks as they are encouraged in my team.	Interpersonal risk-taking
26	In my professional environment, I feel at liberty to express my authentic self.	Interpersonal risk-taking

PSP Version 3

No.	Items	Domains
1	In the team, my abilities and talents are greatly appreciated.	Leadership support
2	I feel empowered to make errors in the workplace without worrying about facing consequences from my colleagues.	Trust/respect
3	None of my colleagues would intentionally behave in a manner that diminishes my contributions.	Trust/respect
4	Seeking assistance from my colleagues is a straightforward process.	Trust/respect
5	We have the capability to address challenges and difficult topics in the workplace.	Organizational/structural support
6	I am well aware of the requirements of my role in the workplace.	Organizational/structural support
7	I am driven to propose innovative ideas to enhance team performance.	Organizational/structural support
8	The team I am engaged with recognizes and respects my creative capabilities.	Team support
9	My colleagues demonstrate a professional openness to diverse perspectives.	Team support
10	My ideas and suggestions receive support from my colleagues.	Team support
11	My colleagues consistently share relevant work-related information.	Team support
12	My colleagues accept diversity and never exclude others for their differences.	Team support
13	Collaborating with my peers ensures that my distinctive skills and talents are recognized and effectively utilized.	Team support
14	In my professional environment, I feel at liberty to express my authentic self.	Interpersonal risk-taking
15	I feel secure taking work-related risks as they are encouraged in my team.	Interpersonal risk-taking

PSP Version 4

No.	Items	Domains
1	In the team, my strengths are greatly appreciated.	Leadership support
2	I feel empowered to make errors in the workplace without worrying about facing consequences from my colleagues.	Trust/respect
3	None of my colleagues would intentionally behave in a manner that diminishes my contributions.	Trust/respect
4	Seeking assistance from my colleagues is a straightforward process.	Trust/respect
5	We have the capability to address difficult situations in the workplace.	Organizational/structural support
6	I am well aware of the requirements of my role in the workplace.	Organizational/structural support
7	My colleagues demonstrate a professional openness to diverse perspectives.	Team support
8	When I suggest new ideas, my colleagues provide support.	Team support
9	Collaborating with my peers ensures that my qualities are valued.	Team support
10	In my professional environment, I feel at liberty to express my authentic self.	Interpersonal risk-taking

Supplementary Table 6

Serbian version (original)

Upitnik za prikupljanje osnovnih socio-demografskih karakteristika

1. **Pol:**
   a) muški
   b) ženski
   c) ne želim da se izjasnim
2. **Bračni status: _____**
3. **Starost: _____**
4. **Godine radnog iskustva: _____**
5. **Nivo obrazovanja:**
   a) osnovne akademske studije (*Bachelor*)
   b) master akademske studije
   c) specijalističke studije
   d) doktorske studije
6. **Radna pozicija (zanimanje) u organizaciji: _____**

Skala percepcije psihološke sigurnosti (PSP)

Molimo Vas da na pitanja odgovorite odabirom jednog od ponuđenih odgovora na skali od 1 do 5, gde 1 označava potpuno neslaganje, a 5 potpuno slaganje sa navedenom tvrdnjom. Molimo Vas da odgovorite na sva pitanja.

Br.	Stavka	Domen
1	U timu se moje snage visoko vrednuju.	Podrška liderstva
2	Osećam da mogu da napravim greške na radnom mestu bez straha od posledica od strane kolega.	Poverenje/poštovanje
3	Nijedan moj kolega ne bi namerno postupao na način koji umanjuje moj doprinos.	Poverenje/poštovanje
4	Traženje pomoći od kolega je jednostavno.	Poverenje/poštovanje
5	Sposoban/na sam da se nosim sa teškim situacijama na radnom mestu.	Organizaciona/strukturna podrška
6	Dobro sam upoznat/a sa zahtevima svoje radne uloge.	Organizaciona/strukturna podrška
7	Moje kolege pokazuju profesionalnu otvorenost prema različitim perspektivama.	Timska podrška
8	Kada predložim nove ideje, moje kolege pružaju podršku.	Timska podrška
9	Saradnja sa kolegama osigurava da se moji kvaliteti prepoznaju.	Timska podrška
10	U svom profesionalnom okruženju osećam slobodu da izrazim svoj autentični identitet.	Interpersonalno preuzimanje rizika

English version (translated)

Questionnaire for collecting basic socio-demographic characteristics

1. **Gender:**
   a) male
   b) female
   c) prefer not to disclose
2. **Marital Status: _____**
3. **Age: _____**
4. **Years of Work Experience: _____**
5. **Level of Education:**
   a) Bachelor's degree
   b) Master's degree
   c) Specialized study
   d) Doctorate degree
6. **Position (Job Title) in Your Organization: _____**

Psychological Safety Perception (PSP) scale

Please respond to the questions by selecting the desired answer from the 5 options provided, indicating the degree of agreement with the given statement, where 1 indicates complete disagreement, and 5 indicates complete agreement with the statement. Please answer all questions.

No.	Items	Domains
1	In the team, my strengths are greatly appreciated	Leadership support
2	I feel empowered to make errors in the workplace without worrying about facing consequences from my colleagues.	Trust/respect
3	None of my colleagues would intentionally behave in a manner that diminishes my contributions.	Trust/respect
4	Seeking assistance from my colleagues is a straightforward process.	Trust/respect
5	We have the capability to address difficult situations in the workplace.	Organizational/structural support
6	I am well aware of the requirements of my role in the workplace.	Organizational/structural support
7	My colleagues demonstrate a professional openness to diverse perspectives.	Team support
8	When I suggest new ideas, my colleagues provide support.	Team support
9	Collaborating with my peers ensures that my qualities are valued.	Team support
10	In my professional environment, I feel at liberty to express my authentic self.	Interpersonal risk-taking

S H O R T R E P O R T

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Visual acuity and anatomical outcomes of intravitreal aflibercept treatment in patients with center-involved diabetic macular edema – a retrospective longitudinal cohort study

Oštrina vida i anatomski ishodi lečenja intravitrealnim afliberceptom kod bolesnika koji imaju centralni dijabetični edem makule – retrospektivna longitudinalna kohortna studija

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Abstract

Background/Aim. Center-involved diabetic macular edema (CI-DME) is a major cause of vision loss in diabetes mellitus, characterized by retinal thickening (1 mm) in the central foveal zone. Intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents, such as aflibercept, are widely used to treat retinal edema and improve visual outcomes. The aim of the study was to evaluate anatomical and functional changes of the retina following intravitreal administration of aflibercept in patients with CI-DME. **Methods.** This retrospective longitudinal cohort study included 70 eyes in 50 patients with optical coherence tomography (OCT)-confirmed CI-DME [with central foveal thickness (CFT) ≥ 350 μm and best-corrected visual acuity (BCVA) ≥ 0.6 Snellen], treated with three monthly aflibercept injections. BCVA, CFT, and macular volume (MV) were measured using the Optovue RTVue XR OCT device at baseline and after 1, 3, and 6 months of treatment. **Results.** Mean patient age was 64.63 ± 7.79 years. Hypertension was the most prevalent comorbidity (72.0%). Over the six-month follow-up period, significant reductions were observed in mean CFT (459.00 μm to 379.92 μm, $p < 0.001$) and MV (9.05 mm³ to 8.44 mm³, $p < 0.001$) values. Although BCVA showed modest improvement, it did not reach statistical significance. Anatomical improvements align with aflibercept's inhibition of VEGF-A and placental growth factor, which reduced vascular permeability. **Conclusion.** Intravitreal aflibercept significantly decreases retinal thickness and MV in patients with CI-DME, confirming its anatomical efficacy. Functional visual improvement was limited, possibly due to chronic retinal damage. In order to clarify the effect of intravitreal aflibercept on visual outcomes, longer-term studies with larger patient cohorts are required.

Keywords:
aflibercept; diabetic retinopathy; intravitreal injections; macular edema; ophthalmologic surgical procedures; tomography, optical coherence; treatment outcome; vascular endothelial growth factors.

Apstrakt

Uvod/Cilj. Dijabetični edem makule koji zahvata centar makule (*center-involved diabetic macular edema* – CI-DME) jedan je od glavnih uzroka gubitka vida kod obolelih od dijabetesa melitusa, a karakteriše ga zadebljanje mrežnjače (1 mm) u centralnoj zoni fovee. Intravitrealni lekovi koji inhibiraju faktor rasta vaskularnog endotela (*anti-vascular endothelial growth factor* – anti-VEGF), kao što je aflibercept, široko se koriste za lečenje edema mrežnjače i poboljšanje ishoda vidnih funkcija. Cilj rada bio je da se procene anatomske i funkcionalne promene mrežnjače nakon intravitrealne primene aflibercepta kod obolelih od CI-DME. **Metode.** Retrospektivnom longitudinalnom kohortnom studijom obuhvaćeno je 70 očiju kod 50 bolesnika koji su imali CI-DME, potvrđen pomoću *optical coherence tomography* – OCT [sa centralnom debljinom fovee (*central foveal thickness* – CFT) ≥ 350 μm i najbolje korigovanom vidnom oštrinom (*best-corrected visual acuity* – BCVA) ≥ 0,6 po Snellen-u], lečenih primenom tri mesečne injekcije aflibercepta. BCVA, CFT i makularni volumen (MV) mereni su na početku tretmana i nakon 1, 3 i 6 meseci pomoću Optovue RTVue XR OCT uređaja.

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Rezultati. Prosečna starost bolesnika iznosila je 64,63 ± 7,79 godina. Hipertenzija je bila najčešća pridružena bolest (72,0%). Tokom šestomesečnog praćenja zabeleženo je značajno smanjenje prosečne vrednosti CFT (sa 459,00 μm na 379,92 μm, $p < 0,001$) i MV (sa 9,05 mm³ na 8,44 mm³, $p < 0,001$). Iako je pokazano blago poboljšanje rezultata BCVA, ono nije dostiglo statističku značajnost. Anatomska poboljšanja bila su u skladu sa inhibicijom VEGF-A i faktora rasta posteljice dejstvom aflibercepta, čime je smanjena vaskularna permeabilnost. **Zaključak.** Intravitrealna primena aflibercepta značajno smanjuje debljinu i MV mrežnjače kod obolelih od CI-DME, potvrđujući njegovu anatomsku efikasnost. Funkcionalno poboljšanje vida bilo je ograničeno, verovatno zbog hroničnog oštećenja mrežnjače. Da bi se razjasnio uticaj intravitrealno primenjenog aflibercepta na ishode vidnih funkcija, potrebne su dugotrajnije studije koje uključuju veći broj bolesnika.

Ključne reči:
aflibercept; dijabetesna retinopatija; injekcije, intravitrealne; žuta mrlja, edem; hirurgija, oftalmološka, procedure; tomografija, optička, koherentna; lečenje, ishod; faktori rasta endotela krvnih sudova.

Introduction

Diabetic macular edema (DME) is characterized by retinal thickening and accumulation of extracellular fluid in the macula. This fluid typically accumulates in retinal layers, including the inner nuclear layer, outer plexiform layer, Henle's fiber layer, and subretinal space. Accurate assessment of DME requires a comprehensive three-dimensional evaluation, traditionally achieved through dilated fundus examination using slit-lamp biomicroscope and/or stereo fundus photography [1, 2].

Current clinical guidelines recommend multiple treatment modalities for DME, including intravitreal anti-vascular endothelial growth factor (VEGF) therapy, laser photocoagulation, and corticosteroid administration. Anti-VEGF agents target VEGF to reduce retinal vascular permeability, thereby decreasing macular edema and improving visual acuity (VA). Laser photocoagulation is primarily employed in non-center-involved DME (CI-DME) to stabilize or reduce edema, whereas corticosteroids are applied to mitigate inflammation and swelling in refractory cases [3].

CI-DME is clinically significant due to retinal thickening affecting the central subfield zone–a 1-mm diameter area centered on the fovea–which is strongly associated with visual impairment [4]. CI-DME necessitates more aggressive treatment, predominantly anti-VEGF therapy, as it represents the leading cause of vision loss among diabetic patients [5]. The global prevalence of DME is estimated at approximately 5.5% among individuals with diabetes mellitus, with no statistically significant difference observed between high-income and low-to-middle-income countries [6].

Diagnosis of DME integrates clinical fundus examination with advanced imaging modalities, including fluorescein angiography (FA), fundus autofluorescence, and optical coherence tomography (OCT). OCT is a non-invasive, non-contact imaging technique that provides high-resolution, cross-sectional retinal images. By analyzing the intensity and depth of reflected light, OCT enables precise localization of pathology within specific retinal layers. This capability facilitates both quantitative assessment of retinal thickness (RT) and qualitative evaluation of individual retinal layer integrity, which holds significant prognostic value for treatment response. Baseline disorganization of retinal inner layers (DRIL), hyperreflective foci, and the disruption of the external limiting membrane, ellipsoid zone, and cone outer segment tip have been associated with poorer VA, whereas post-treatment restoration correlates with VA improvement. In contrast, cystoid edema and serous detachment are predictive of significant thickness reduction [7].

Aflibercept (2 mg; Eylea®), a recombinant fusion protein that inhibits VEGF-A, VEGF-B, and placental growth factor (PlGF), has been approved by the United States Food and Drug Administration – FDA [8] and the European Medicines Agency – EMA [9] since 2012 for DME treatment.

The present study aims to evaluate functional outcomes, specifically best-corrected VA (BCVA) and morphological changes assessed by OCT parameters – central foveal thickness (CFT) and macular volume (MV) in patients with CI-DME treated with intravitreal aflibercept.

Methods

This retrospective longitudinal cohort study was conducted at the Clinic for Eye Diseases, Clinical Hospital Center "Zvezdara", Belgrade, Serbia, from April 2022 to February 2025. This study adhered to the tenets of the Declaration of Helsinki and Good Clinical Practice guidelines. The study was approved by the Ethics Committee of the Clinical Hospital Center "Zvezdara" (No. 02/10/2025, from October 06, 2025).

The study included 70 eyes in 50 patients diagnosed with CI-DME who were treated with intravitreal aflibercept. The unit of observation in this study was the eye, so when a patient received intravitreal treatment in both eyes, this was analyzed as two separate units of observation.

The eligibility criteria were defined by the Republic Health Insurance Fund, which covered treatment costs for patients meeting the following criteria: FA-confirmed macular leakage, OCT-measured CFT ≥ 350 μm, BCVA ≥ 0.6 (Snellen chart), and glycated hemoglobin (HbA1c) ≤ 8%. Exclusion criteria included: BCVA < 0.6, CFT < 350 μm, HbA1c > 8%, concomitant ocular pathologies (such as exudative age-related macular degeneration, retinal vascular occlusions, or retinal detachment), myocardial infarction or stroke within the previous 6 months, ocular or periocular inflammation, pregnancy, and age < 18 years.

Patients received intravitreal injections (IVIs) of aflibercept 2 mg (Eylea®, Bayer AG, Germany), approved by the National Health Fund for DME. The treatment protocol consisted of three consecutive monthly injections. Primary outcome measures included BCVA, CFT, and MV, recorded at baseline and 1, 3, and 6 months after the treatment.

All patients underwent a comprehensive ophthalmologic evaluation, including OCT and FA. OCT imaging was performed using the RTVue XR Avanti (Optovue Inc., Fremont, CA, USA) to measure MV and CFT. FA was conducted with the VisuCam 500 (Carl Zeiss, Germany) according to standard protocols.

Statistical analyses were performed using IBM SPSS Statistics 26.0. Categorical variables were summarized as frequencies and analyzed using the Chi-square test. Continuous variables were expressed as mean ± standard deviation. Normality was assessed using the Kolmogorov-Smirnov test. Repeated measures analysis of variance with Bonferroni correction was applied for longitudinal comparisons. A p-value < 0.05 was considered statistically significant.

Results

A total of 70 eyes in 50 patients with confirmed type 2 diabetes mellitus were included in the analysis. The study population comprised 27 men (54.0%) and 23 women (46.0%), with a mean age of 64.63 ± 7.79 years. All 70 eyes received intravitreal aflibercept treatment, including 31 right eyes (44.3%) and 39 left eyes (55.7%). IVIs were administered in both eyes in 20 (40.0%) patients, accounting for 40 (57.1%) of all treated eyes. IVIs were administered in one eye in 30 (60.0%) patients. Hypertension was the most prevalent comorbidity, present in 36 (72.0%) patients, followed by hyperlipidemia in 7 (14.0%) patients. Other comorbidities, recorded in 7 separate cases, included hypothyroidism (n = 2), deep vein thrombosis (n = 2), cerebrovascular insult (n = 1), epilepsy (n = 1), and chronic kidney disease (n = 1). All participants had at least one comorbidity (Table 1).

The mean CFT showed a statistically significant reduction over time, decreasing from 459.00 µm at baseline to 351.33 µm at 3 months, and remaining stable at 379.92 µm at 6 months ($p < 0.001$). Similarly, mean MV decreased significantly from 9.05 mm³ at baseline to 8.44 mm³ at 6 months ($p < 0.001$). BCVA demonstrated a slight but non-significant improvement compared to baseline (0.66 vs. 0.70; $p = 0.688$), with minor fluctuations across follow-up visits. After aflibercept treatment, CFT and MV decreased significantly ($p < 0.001$), indicating sustained anatomical improvement, while BCVA showed mild, non-significant fluctuations over 6 months ($p = 0.688$) (Table 2).

Table 1

Baseline characteristics of study patients

Characteristic	Value
Participants	50
Eyes included	70
Sex	
men	27 (54.00)
women	23 (46.00)
Age, years	64.63 ± 7.79
Treated eyes	
right	31 (44.30)
left	39 (55.70)
Patients receiving injections in both eyes (all patients)	20 (40.00)
Eyes treated bilaterally (all treated eyes)	40 (57.10)
Comorbidities	
hypertension	36 (72.00)
hyperlipidaemia	7 (14.00)
other comorbidities	7 (14.00)

All values are given as numbers (percentages) or mean ± standard deviation.

Table 2

Anatomical and functional outcome in patients with center-involved diabetic macular edema treated by aflibercept

Reference point	CFT, µm	MV, mm³	BCVA
Baseline	459.00 (436.29–451.74)	9.05 (8.74–9.37)	0.66 (0.62–0.70)
After the loading dose			
at 1 month	344.17 (325.24–363.10)	7.99 (7.76–8.21)	0.72 (0.66–0.78)
at 3 months	351.33 (322.91–379.76)	8.10 (7.81–8.38)	0.71 (0.64–0.79)
at 6 months	379.92 (344.77–414.87)	8.44 (8.09–8.79)	0.70 (0.64–0.77)
p-value	< 0.001	< 0.001	0.688

CFT – central foveal thickness; MV – macular volume; BCVA – best-corrected visual acuity.
All values are given as mean (95% confidence interval).

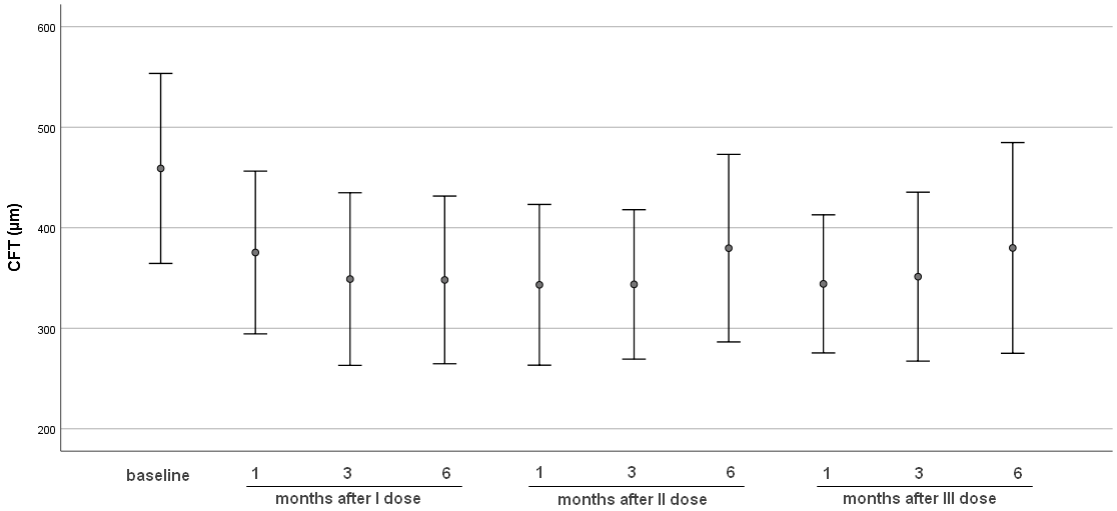

Fig. 1 – Mean values of central foveal thickness (CFT) before and after treatment administration. All values are given as mean ± standard deviation.

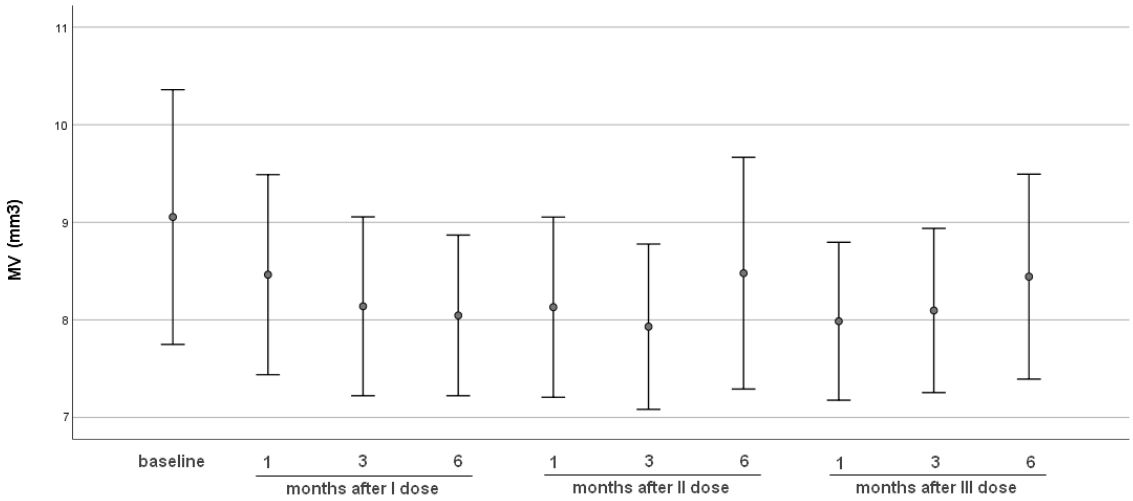

Fig. 2 – Mean values of macular volume (MV) before and after treatment administration. All values are given as mean ± standard deviation.

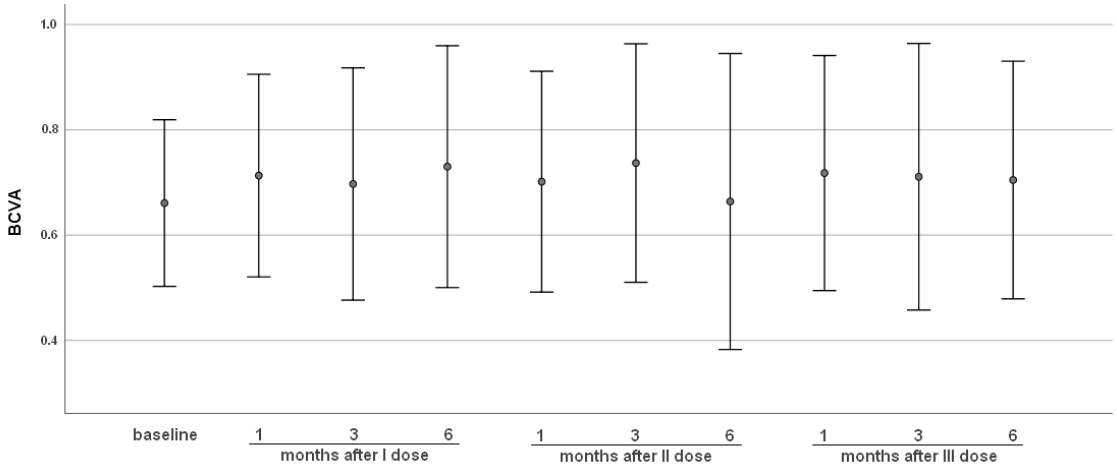

Fig. 3 – Mean values of best-corrected visual acuity (BCVA) before and after treatment administration. All values are given as mean ± standard deviation.

Comparing pre- and post-treatment metrics revealed a significant reduction in both CFT and MV, whereas BCVA remained statistically unchanged (Figures 1–3).

Baseline CFT was significantly higher than at all subsequent time points, decreasing from 459.00 µm to 379.92 µm at 6 months after the third dose (Table 3). It is

Table 3

The values of monitored parameters

Parameter/Time point	Mean (SD)	*p*-value
CFT, μm		
BL	459.00 (94.53)	
I1	375.38 (80.97)	
I3	348.94 (85.87)	
I6	348.12 (83.42)	
II1	343.24 (79.97)	
II3	343.65 (74.34)	< 0.001
II6	379.68 (93.30)	
III1	344.17 (68.69)	
III3	351.33 (84.01)	
III6	379.92 (104.82)	
Total	369.50 (92.26)	
MV, mm³		
BL	9.05 (1.30)	
I1	8.46 (1.03)	
I3	8.14 (0.92)	
I6	8.05 (0.82)	
II1	8.13 (0.92)	
II3	7.93 (0.85)	< 0.001
II6	8.48 (1.19)	
III1	7.99 (0.81)	
III3	8.10 (0.84)	
III6	8.44 (1.05)	
Total	8.30 (1.04)	
BCVA		
BL	0.66 (0.16)	
I1	0.71 (0.19)	
I3	0.70 (0.22)	
I6	0.73 (0.23)	
II1	0.70 (0.21)	
II3	0.74 (0.23)	0.688
II6	0.66 (0.28)	
III1	0.72 (0.22)	
III3	0.71 (0.25)	
III6	0.70 (0.23)	
Total	0.70 (0.22)	

SD – standard deviation; CFT – central foveal thickness; BL – baseline; MV – macular volume; BCVA – best-corrected visual acuity.
All values are given as mean (SD).
***Note*: Roman numerals indicate the first (I), second (II), and third (III) dose, and Arabic numerals indicate months (1, 3, 6) after each dose.**

noteworthy that 6 months after the second dose, there was another increase in CFT, although the value remained lower than before treatment (459.00 vs. 379.68). Following the third dose, CFT decreased again, with a slight rise 6 months after the third dose. A similar trend was observed in MV, decreasing from 9.05 mm³ to 8.44 mm³, with minor increases recorded at the same intervals as CFT – 6 months after the second and third doses.

Tables 4 and 5 present the results after the Bonferroni correction, showing that differences in CFT and MV were

Table 4

***Post hoc* comparison of central foveal thickness**

Comparison	Mean (95% CI)	*p*-value
BL vs. I1	83.621 (34.05–133.19)	< 0.001
BL vs. I3	110.061 (62.15–157.97)	< 0.001
BL vs. I6	110.881 (56.42–165.34)	< 0.001
BL vs. II1	115.762 (67.27–164.26)	< 0.001
BL vs. II3	115.346 (64.24–166.45)	< 0.001
BL vs. II6	79.324 (21.01–137.63)	< 0.001
BL vs. III1	114.830 (64.00–165.66)	< 0.001
BL vs. III3	107.667 (50.45–164.88)	< 0.001
BL vs. III6	79.081 (22.38–135.79)	< 0.001
I1 vs. I3	26.440 (-23.65–76.53)	1.000
I1 vs. I6	27.260 (-29.12–83.64)	1.000
I1 vs. II1	32.141 (-18.50–82.78)	1.000
I1 vs. II3	31.725 (-21.42–84.87)	1.000
I1 vs. II6	-4.297 (-64.40–55.81)	1.000
I1 vs. III1	31.209 (-21.67–84.09)	1.000
I1 vs. III3	24.046 (-35.00–83.09)	1.000
I1 vs. III6	-4.540 (-63.09–54.01)	1.000
I3 vs. I6	0.820 (-54.11–55.75)	1.000
I3 vs. II1	5.701 (-43.32–54.72)	1.000
I3 vs. II3	5.286 (-46.32–56.89)	1.000
I3 vs. II6	-30.737 (-89.48–28.01)	1.000
I3 vs. III1	4.770 (-46.56–56.10)	1.000
I3 vs. III3	-2.394 (-60.05–55.26)	1.000
I3 vs. III6	-30.980 (-88.13–26.17)	1.000
I6 vs. II1	4.881 (-50.55–60.32)	1.000
I6 vs. II3	4.465 (-53.27–62.20)	1.000
I6 vs. II6	-31.557 (-95.76–32.64)	1.000
I6 vs. III1	3.949 (-53.54–61.44)	1.000
I6 vs. III3	-3.214 (-66.42–59.99)	1.000
I6 vs. III6	-31.800 (-94.54–30.94)	1.000
II1 vs. II3	-0.416 (-52.56–51.72)	1.000
II1 vs. II6	-36.438 (-95.66–22.78)	1.000
II1 vs. III1	-0.932 (-52.80–50.94)	1.000
II1 vs. III3	-8.095 (-66.24–50.05)	1.000
II1 vs. III6	-36.681 (-94.32–20.96)	1.000
II3 vs. II6	-36.023 (-97.40–25.35)	1.000
II3 vs. III1	-0.516 (-54.83–53.80)	1.000
II3 vs. III3	-7.679 (-68.02–52.66)	1.000
II3 vs. III6	-36.265 (-96.12–23.59)	1.000
II6 vs. III1	35.507 (-25.64–96.65)	1.000
II6 vs. III3	28.343 (-38.21–94.89)	1.000
II6 vs. III6	-0.242 (-66.35–65.87)	1.000
III1 vs. III3	-7.164 (-67.27–52.94)	1.000
III1 vs. III6	-35.749 (-95.37–23.87)	1.000
III3 vs. III6	-28.586 (-93.73–36.56)	1.000

BL – baseline; CI – confidence interval. All values are given as mean (95% CI).

***Note*: Results of the Bonferroni-corrected correlation analysis. Roman numerals indicate the first (I), second (II), and third (III) dose, and Arabic numerals indicate months (1, 3, 6) after each dose.**

Table 5

***Post hoc* comparison of macular volume**

Comparison	Mean (95% CI)	*p*-value
BL vs. I1	0.59064 (0.0108–1.1705)	0.040
BL vs. I3	0.91437 (0.3539–1.4748)	< 0.001
BL vs. I6	1.00820 (0.3712–1.6452)	< 0.001
BL vs. II1	0.92328 (0.3561–1.4905)	< 0.001
BL vs. II3	1.12334 (0.5256–1.7211)	< 0.001
BL vs. II6	0.57538 (-0.1066–1.2574)	0.264
BL vs. III1	1.06788 (0.4734–1.6624)	< 0.001
BL vs. III3	0.95780 (0.2886–1.6270)	< 0.001
BL vs. III6	0.61067 (-0.0526–1.2739)	0.120
I1 vs. I3	0.32373 (-0.2621–0.9096)	1.000
I1 vs. I6	0.41756 (-0.2419–1.0771)	1.000
I1 vs. II1	0.33264 (-0.2597–0.9250)	1.000
I1 vs. II3	0.53270 (-0.0889–1.1543)	0.231
I1 vs. II6	-0.01525 (-0.7183–0.6878)	1.000
I1 vs. III1	0.47724 (-0.1413–1.0958)	0.526
I1 vs. III3	0.36716 (-0.3235–1.0578)	1.000
I1 vs. III6	0.02003 (-0.6648–0.7049)	1.000
I3 vs. I6	0.09383 (-0.5487–0.7363)	1.000
I3 vs. II1	0.00891 (-0.5644–0.5822)	1.000
I3 vs. II3	0.20897 (-0.3946–0.8125)	1.000
I3 vs. II6	-0.33898 (-1.0261–0.3481)	1.000
I3 vs. III1	0.15351 (-0.4469–0.7539)	1.000
I3 vs. III3	0.04343 (-0.6310–0.7178)	1.000
I3 vs. III6	-0.30370 (-0.9722–0.3648)	1.000
I6 vs. II1	-0.08492 (-0.7333–0.5635)	1.000
I6 vs. II3	0.11514 (-0.5601–0.7904)	1.000
I6 vs. II6	-0.43282 (-1.1837–0.3181)	1.000
I6 vs. III1	0.05968 (-0.6128–0.7321)	1.000
I6 vs. III3	-0.05040 (-0.7897–0.6889)	1.000
I6 vs. III6	-0.39753 (-1.1314–0.3364)	1.000
II1 vs. II3	0.20006 (-0.4098–0.8099)	1.000
II1 vs. II6	-0.34789 (-1.0406–0.3448)	1.000
II1 vs. III1	0.14460 (-0.4621–0.7513)	1.000
II1 vs. III3	0.03452 (-0.6455–0.7146)	1.000
II1 vs. III6	-0.31261 (-0.9868–0.3616)	1.000
II3 vs. II6	-0.54795 (-1.2658–0.1699)	0.568
II3 vs. III1	-0.05546 (-0.6908–0.5799)	1.000
II3 vs. III3	-0.16553 (-0.8713–0.5402)	1.000
II3 vs. III6	-0.51267 (-1.2127–0.1874)	0.750
II6 vs. III1	0.49249 (-0.2227–1.2077)	1.000
II6 vs. III3	0.38242 (-0.3960–1.1608)	1.000
II6 vs. III6	0.03529 (-0.7380–0.8086)	1.000
III1 vs. III3	-0.11007 (-0.8131–0.5929)	1.000
III1 vs. III6	-0.45721 (-1.1545–0.2401)	1.000
III3 vs. III6	-0.34713 (-1.1091–0.4149)	1.000

BL – baseline; CI – confidence interval.
All values are given as mean (95% CI).
***Note*: Results of the Bonferroni-corrected correlation analysis. Roman numerals indicate the first (I), second (II), and third (III) dose, and Arabic numerals indicate months (1, 3, 6) after each dose.**

significant across all time points. BCVA remained consistently higher compared to baseline across all time points, with a minor decrease recorded 6 months after the second dose.

Discussion

This retrospective longitudinal cohort study demonstrated that intravitreal aflibercept effectively reduces CFT and MV in patients with CI-DME. These findings are consistent with prior clinical trials and real-world studies, which similarly report significant anatomical improvements following aflibercept therapy. Real-world studies and randomized clinical trials have shown comparable decreases in CFT, typically ranging from 150 to 250 μm after the initial loading phase, followed by sustained anatomical improvement during maintenance treatment [10, 11]. The observed mean CFT reduction of approximately 79 μm at 6 months is somewhat smaller than those reported in pivotal trials; the reported CFT range in literature was 100 μm – 250 μm with significant decreases after initial treatment phases. This effect is attributed to aflibercept's high binding affinity for VEGF-A and PlGF, leading to decreased vascular permeability and resolution of intraretinal and subretinal fluid [11].

A significant association between reductions in CFT and improvements in BCVA has been reported, although the relationship is not strictly proportional. Persistent structural changes, such as DRIL or photoreceptor damage, may limit functional recovery despite substantial anatomical improvement. Overall, the decrease in CFT observed with aflibercept therapy represents a reliable anatomical biomarker of treatment response in DME and reinforces its role as a first-line anti-VEGF agent in managing center-involved disease [12, 13].

In our daily clinical practice, as well as in the current study, mean baseline MV typically ranges between 10.0 mm³ and 11.5 mm³, ultimately decreasing to approximately 7.5–8.5 mm³ at 12 months post-treatment. Munayco-Guillén et al. [14] reported a mean reduction from 10.8 mm³ to 9.3 mm³, corresponding to about 14% decrease 12 months after treatment. Similarly, Lukic et al. [11] demonstrated a progressive decline in MV parallel to a decrease in CFT, with the most substantial anatomical response occurring after the initial administration phase, followed by stabilization during maintenance injections.

This anatomical improvement is attributed to aflibercept's dual inhibition of VEGF-A and PlGF, leading to decreased vascular permeability, reduced extracellular fluid accumulation, and restoration of macular architecture. The reduction in MV closely correlates with improved BCVA in most studies, although the relationship is not strictly linear. Chronic macular ischemia, DRIL, and photoreceptor loss may limit visual recovery despite significant anatomical resolution [13]. Meta-analyses indicate that switching refractory DME from bevacizumab or ranibizumab to aflibercept leads to significant improvement in VA and reductions in macular thickness, with sustained efficacy and acceptable safety up to 12 months [15].

The consistent reduction in MV observed across both randomized clinical trials and real-world cohorts underscores its value as a quantitative biomarker of treatment response. Regular OCT assessment of MV and CFT offers an objective approach to monitoring disease activity and tailoring dosing intervals [16]. Overall, the decrease in MV following aflibercept treatment confirms its strong efficacy in improving retinal structure and maintaining visual stability in patients with CI-DME. Some authors demonstrated aflibercept efficacy even in DME treatment in so-called nonresponders to bevacizumab [17]. Systematic review and correlation analyses suggest MV may serve as a surrogate biomarker for VA in DME, showing moderate endpoint correlation but no significant treatment-effect correlation, thereby requiring cautious interpretation [18].

Compared with the APOLLON study [19], which reported a moderate, yet statistically significant improvement in BCVA [+5–8 Early Treatment of Diabetic Retinopathy Study (ETDRS) letters] at 12 months, our findings show stable, non-significant BCVA changes over 6 months despite pronounced anatomical improvement. Differences in follow-up duration and in the methodology of VA assessment should be acknowledged, as BCVA in this study was measured using Snellen charts rather than ETDRS.

One study has shown modest improvements in VA within the first year of treatment [20], which was also confirmed in our cohort. However, this improvement is inconsistent and tends to diminish over time. In line with our findings, the same study reported a significant decrease in CFT [20]. In this study, some parameters that were observed in our study were not reported. In everyday clinical practice, compared to controlled trial settings, the treatment effects on VA are less pronounced [20, 21]. In general, similar observations were shown in a 2022 meta-analysis [22]. The slightly better outcomes reported in that study, compared to our results, may be explained by the higher number of injections administered. While our patients received three doses, their study reported up to eight doses [23]. As we similarly found, MV after the treatment showed a significant decrease in other studies [23, 24]. This can be attributed to the reduction of macular exudation and central RT under treatment. Therefore, this reduction in MV increased gradually from 15% at 6 months to 25% at 12 months [25].

Considering the significance of DME as a leading cause of irreversible visual impairment in the diabetic population, early detection and timely treatment, including anti-VEGF therapy, are key steps toward slowing disease progression and preserving functional vision. Clinical studies have shown that administration of aflibercept leads to improvement in VA within the first year of treatment. In a multicenter study, Korobelnik et al. [21] reported an average increase of 10–12 letters in BCVA at 52 weeks, with a significant reduction in central RT. Our results have also shown a morphological response, although without statistically significant functional improvement. After 100

weeks of follow-up, Brown et al. [26] confirmed the durability of the obtained functional improvement, with an emphasis on continuous treatment. By analyzing the results at 148 weeks, Heier et al. [27] confirmed that the effect of the treatment can be preserved long-term. However, they also observed that in certain patients, the effects decreased progressively. Our findings are partially consistent with theirs, as our study also showed a slight increase in morphological parameters after the second dose, which was corrected after the third aflibercept administration. In the AURIGA study, Donati et al. [20] recorded a clinically significant decrease in CFT and a slight improvement in BCVA in a 24-month real-world setting, while highlighting a high variability in treatment response. Similar observations were reported in the study by Santhakumaran et al. [22]. This meta-analysis found that the number of administrations and earlier initiation of treatment are key factors in anti-VEGF therapy success. The aforementioned studies achieved better results compared to our findings, most likely because their patients received up to eight doses within the first year, while ours were given only three. Korobelnik et al. [21] confirmed that more intensive treatment regimens yield more prominent and stable responses, especially in early-stage cases. Griffin et al. [23] state that secondary neurodegenerative retinal impairments, which are common in elderly patients with long-term DME, may limit the potential for full recovery of the visual function, despite anatomical improvement. This may explain the absence of a more significant functional improvement in our sample. In line with our findings, a significant reduction in MV has been widely reported in the literature. Donati et al. [20] observed a progressive decline in MV, reporting a 15% reduction at 6 months that extended to 25% at the 12-month follow-up. Tran et al. [25] additionally demonstrated that the treatment response remains positive even in vitrectomized eyes, although with a potentially different dynamic.

Most studies worldwide consider the eye, rather than the patient, as the unit of analysis when evaluating treatment effects [28–32].

Limitations of this study

Limitations of this study include the relatively short follow-up period (other studies track patients for up to 5 years), a fixed three-dose regimen (other studies include more doses), and the lack of stratification by prior treatment (i.e., naïve vs. previously treated with corticosteroids or other anti-VEGF agents). The study analyzed 70 eyes in 50 patients. The statistical approach did not account for interocular correlation, which may be a significant limitation of the study. However, treatment is administered individually to each eye. When both eyes are treated, the results can be quite different.

Conclusion

Intravitreal administration of aflibercept results in a significant reduction in retinal thickness and macular volume in patients with center-involved diabetic macular edema, thereby confirming its anatomical efficacy. This decrease in macular edema is critical for preventing further retinal damage and preserving retinal architecture. However, the observed functional improvement, as measured by best-corrected visual acuity, was limited in this cohort. This limited visual recovery may be attributed to chronic retinal changes and irreversible structural damage, such as photoreceptor loss and disruption of retinal layers, which likely predated treatment initiation.

Given the complex and progressive nature of center-involved diabetic macular edema, longer-term studies with larger patient populations are necessary to better elucidate the relationship between anatomical improvements and functional visual outcomes following aflibercept therapy. Future research should also investigate optimal dosing regimens, the timing of intervention, and potential combination therapies to enhance visual rehabilitation. Such data will be essential for developing personalized treatment protocols aimed at maximizing visual function in patients with center-involved diabetic macular edema.

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Pleural hydatidosis secondary to intrapulmonary echinococcosis

Pleuralna hidatidoza kao posledica intrapulmonalne ehinokokoze

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Abstract

Introduction. Hydatid cysts are most often found in the liver and lungs, while other locations are rarely involved. Pleural hydatidosis, whether primary or secondary, is rarely seen in clinical practice. **Case report.** In this article, we present a case of a 33-year-old woman who presented with cough and dyspnea. Initial chest X-ray showed a large right-sided pleural effusion. Pleural hydatidosis was suspected based on the findings of the computed tomography scan of the chest. Right thoracotomy and cystectomy were performed. Albendazole was administered postoperatively for 6 months, and during this period, liver function tests and abdominal ultrasonography showed no abnormalities. **Conclusion.** This case emphasizes that pleural hydatidosis should be suspected in patients with pleural effusions and large cystic formations found on imaging, especially in endemic areas.

Keywords:
albendazole; diagnosis; echinococcosis; montenegro; pleura; tomography, x-ray computed.

Apstrakt

Uvod. Hidatidne ciste se najčešće nalaze u jetri i plućima, dok su druga mesta retko zastupljena. Pleuralna hidatidoza, bilo primarna ili sekundarna, retko se viđa u kliničkoj praksi. **Prikaz bolesnika.** U ovom radu prikazana je bolesnica stara 33 godine, koja se javila na pregled zbog kašlja i otežanog disanja. Prvi rendgenski snimak grudnog koša pokazao je veliki pleuralni izliv sa desne strane. Na pleuralnu hidatidozu posumnjalo se na osnovu nalaza kompjuterizovane tomografije grudnog koša. Na desnoj strani grudnog koša izvršene su torakotomija i cistektomija. Albendazol je primenjivan postoperativno tokom šest meseci, a tokom tog perioda testovima za ispitivanje funkcije jetre i ultrazvukom abdomena nisu utvrđene abnormalnosti. **Zaključak.** Ovaj slučaj naglašava da na pleuralnu hidatidozu treba posumnjati kod bolesnika sa pleuralnim izlivima i velikim cističnim formacijama uočenim na radiološkim snimcima, naročito u endemskim područjima.

Ključne reči:
albendazol; dijagnoza; ehinokokoza; crna gora; pleura; tomografija, kompjuterizovana, rendgenska.

Introduction

Hydatidosis is an endemic parasitic disease most often caused by *Echinococcus* (*E.*) *granulosus* [1]. People accidentally become infected by consuming contaminated food or through direct contact with a diseased host [2, 3]. The most commonly affected organs are the liver and lungs, but the parasite can be found in almost any organ in the body [4]. Pleural involvement is of rare occurrence. Primary pleural echinococcosis is an exceptionally rare entity within the spectrum of human cystic echinococcosis (less than 1%) [5]. In clinical practice, it is imperative to clearly distinguish between the primary and secondary forms of the disease to eliminate diagnostic ambiguity. Unlike secondary pleural echinococcosis, which occurs as a complication following the rupture of fertile pulmonary or hepatic hydatid cysts (HCs) and the subsequent release of their contents into the pleural space, the primary form involves the direct development of cysts within the pleural cavity itself [5–7]. In this manifestation, the echinococcal development occurs *de novo*, without prior involvement or concurrent pathological changes in the lung or liver parenchyma. This pathophysiological distinction is essential for understanding the pathogenesis of the presented case and underscores its unique clinical significance. HCs are often accidentally detected during radiological examinations. Spontaneous or traumatic cyst rupture most of the time leads to symptoms such as cough, fever, chest pain, dyspnea, and rarely anaphylactic shock [8].

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We present a case of a patient with pleural hydatidosis, which occurred as a complication of spontaneous cyst rupture into the pleural cavity.

Case report

A 33-year-old female patient from the Roma population of the central region of Montenegro was admitted to the Department of Thoracic Surgery, Clinical Center of Montenegro, Podgorica, Montenegro, due to progressive dyspnea lasting one year prior to hospitalization and a persistent non-productive cough lasting 6 months prior to hospitalization. The patient was an active smoker (3.5 pack-years) with no prior comorbidities. Upon admission, physical examination of the chest revealed dullness to percussion and the absence of breath sounds on the right side. Laboratory findings were as follows: erythrocytes 4.47 × 10^{12}/L [reference range (RR): 3.90–5.20 × 10^{12}/L], hemoglobin 139 g/L (RR: 120–153 g/L), leukocytes 23.84 × 10^{9}/L (RR: 3.7–10.0 × 10^{9}/L), neutrophils 22.23 × 10^{9}/L (RR: 1.60–5.80 × 10^{9}/L), eosinophilic granulocytes 0.02 × 10^{9}/L (RR: 0.02–0.50 × 10^{9}/L), platelet count 257 × 10^{9}/L (RR: 150–410 × 10^{9}/L), erythrocyte sedimentation rate 68 mm/h [normal value (NV) < 20 mm/h], glucose 5.5 mmol/L (RR: 4.6–6.4 mmol/L), urea 1.9 mmol/L (RR: 3.5–7.2 mmol/L), creatinine 46 μmol/L (RR: 44–80 μmol/L), aspartate aminotransferase 12 U/L (NV: < 31 U/L), alanine aminotransferase 10 U/L (NV: < 33 U/L), lactate dehydrogenase 138 U/L (RR: 135–225 U/L), creatine kinase 43 U/L (NV: < 190 U/L), C-reactive protein 117.91 mg/dL (NV: < 5 mg/dL).

Serological testing [enzyme-linked immunosorbent assay (ELISA) echinococcus immunoglobulin (Ig) G > 15 U/mL] was positive (NV: negative < 9, equivocal 9–11, positive > 11 U/mL), confirming the suspicion of a parasitic etiology. Forced spirometry: forced vital capacity (FVC) 1.58 L (47%) (NV: 3.36 L; ≥ 80%), forced expiratory volume in 1 sec (FEV1) 1.39 L (48%) (NV: 2.90 L; ≥ 80%), which indicated severe damage to lung function.

The bronchoscopy finding indicated that the vocal cords, trachea, and main carina appeared healthy (normal). Except for signs of extramural compression in the right principal and the *bronchus intermedius*, starting from the main carina, which was deviated to the left, the rest of the endoscopic findings were normal.

An initial chest X-ray and then a computed tomography (CT) scan were performed three weeks before hospitalization. Chest X-ray showed uniform opacity of the right hemithorax with a leftward mediastinal shift, indicating a massive pleural effusion (Figure 1). A subsequent contrast-enhanced multislice CT (MSCT) scan of the chest (Figure 2a, b) revealed a complex radiological presentation: a small pleural effusion 10 mm in the right pleural cavity containing multiple cystic formations. Additionally, three oval cystic formations were visualized within the parenchyma of the upper and middle lobes of the right lung. The largest cyst (6 cm in diameter) was located in the upper lobe, and a smaller one (4.5 cm) in the middle lobe was in direct contact with the visceral pleura. The liver was markedly enlarged, with a 5.5 × 4 cm cystic lesion in segment VI (Figure 3).

Abdominal ultrasound indicated the presence of a cyst in segment VI of the liver (6 × 4 cm), which was drained percutaneously at the same time, followed by sclerosing with ethoxysclerol. The aspirate samples were sent for microbiological and serological testing. Given the extent of the lesions, surgical exploration *via* right lateral thoracotomy was indicated. Intraoperatively, a small serous pleural effusion was identified (biochemical profiling was consistent with exudate, and cytology was negative for malignant cells).

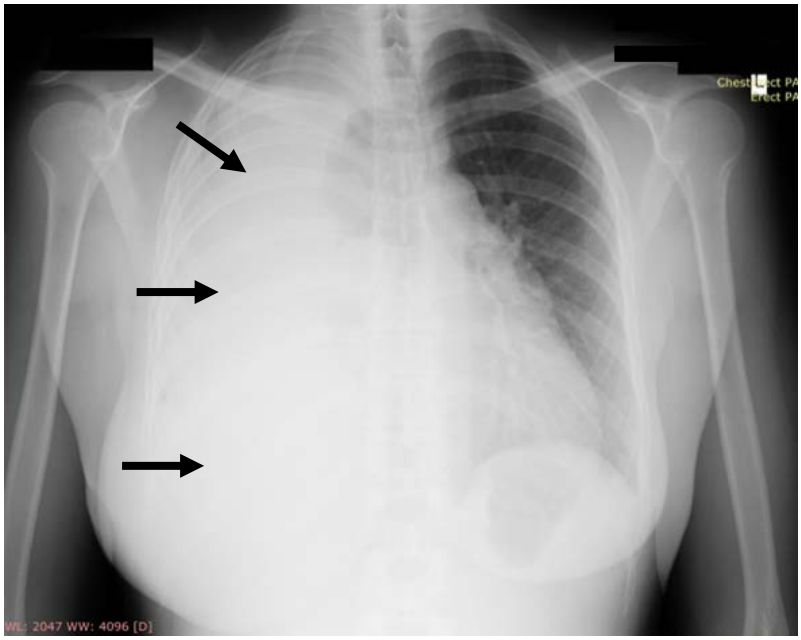

Fig. 1 – Chest X-ray showing uniform opacity of the right hemithorax (arrows).

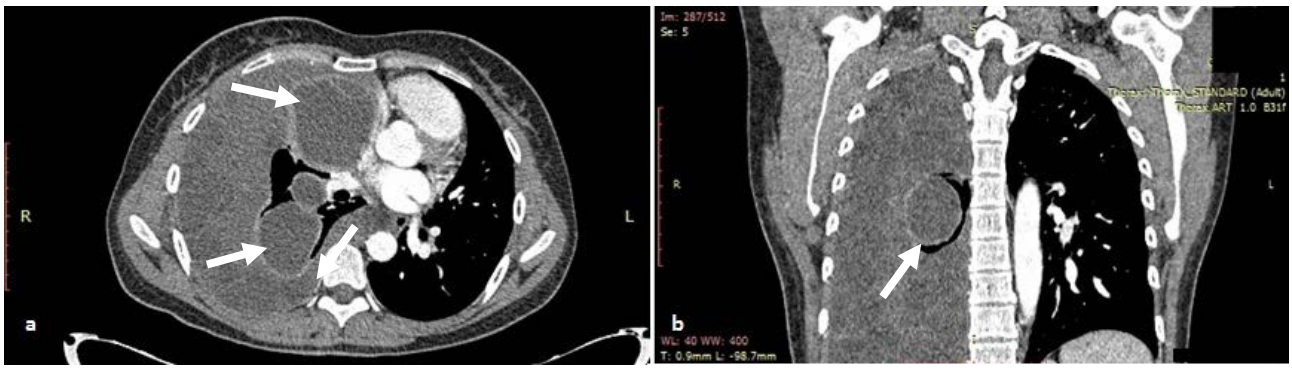

Fig. 2 – Chest computed tomography scan: a) axial view and b) coronal view, showing cystic formations in the right pleural space and in the upper and middle lobes of the right lung (arrows).

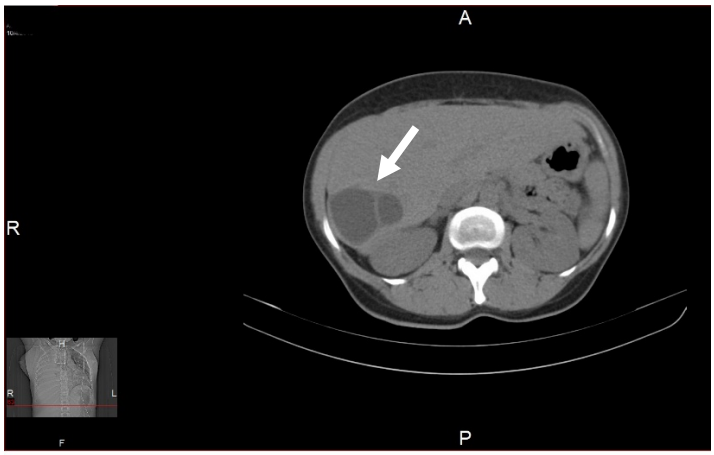

Fig. 3 – Chest computed tomography and upper abdomen scan showing cystic formation in segment VI of the liver (arrow).

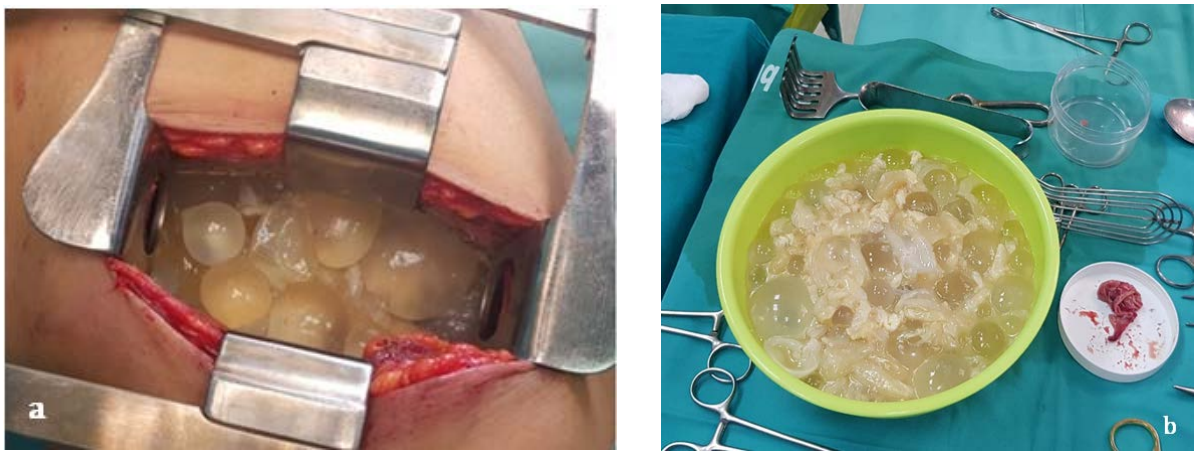

Fig. 4 – Open lateral thoracotomy showing numerous hydatid cysts: a) within the pleural space and b) evacuated from the pleural space.

Multiple intact, firm cystic formations (over 150) were found within the pleural space (Figure 4a, b) and were subsequently evacuated (Figure 5). A thorough inspection of the lung identified three intraparenchymal cysts in the upper and middle lobes. The largest cyst in the upper lobe showed evidence of prior rupture into the pleural space, with several cystobronchial fistulas, which were repaired using 4-0 polydioxanone sutures. Endocystectomy, partial pericystectomy, and lung decortication were performed. Histopathological analysis confirmed the presence of fertile elements (scolices). The postoperative recovery was uneventful. Adjuvant therapy with albendazole was initiated at a dose of 400 mg twice daily for 28 days, followed by a 14-day drug-free interval, for a total of six

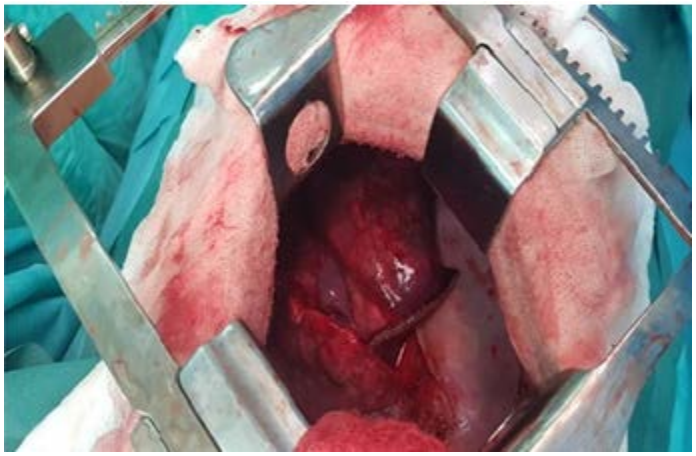

Fig. 5 – Open lateral thoracotomy after removal of hydatid cysts and capitonnage.

cycles.During the treatment period, liver function tests and abdominal ultrasonography were performed monthly. The initially described liver cysts (type CE1, up to 6 × 4 cm) showed regression and transitioned to inactive stages (types CE4/CE5) after 6 months of therapy. A follow-up chest MSCT scan at 6 months demonstrated complete lung re-expansion with no signs of disease recurrence.

Discussion

Hydatid disease is a parasitic disease that usually occurs in younger patients and is most often caused by *E. granulosus* [9]. Echinococcosis is a zoonosis with two hosts, a transitional host (e.g., sheep) and a definitive host (e.g., dogs) [2]. The life cycle of *E. granulosus* does not necessarily involve humans. People are accidentally infected by eating contaminated food or by direct contact with an infected host [2, 3]. HCs usually involve the liver or lungs, but simultaneous involvement of both organs has also been described [4, 10, 11]. After being introduced into the organism orally, the embryo enters the portal circulation. It is carried by the bloodstream to the liver, which is, in most cases, the first destination of the parasite [6]. The possibility of hematogenous or lymphogenous dissemination means that the parasite can be found in almost any other organ. By entering the lymphatic vessels of the stomach, the parasite can reach the thoracic lymphatic duct and so directly travel into the pleura, resulting in primary pleural hydatidosis, which is very rare (< 1%) [11, 12]. Secondary pleural hydatidosis is most often caused by transdiaphragmatic contamination of the pleural space by cysts located in the right upper lobe of the liver or by rupturing of the peripheral lung cysts, and can manifest as pleural HCs or as a parasitic pleural effusion, which is rare in clinical practice [2]. In both cases, HCs can survive and grow within the avascular layers of the pleura due to the specific structure of their membranes, which enable diffusion and active transport of substances necessary for metabolic processes [1]. HC of the lung that is close to the pleural surface can cause thinning of the adventitia and can rupture into the pleural cavity [11]. This may initially go clinically unnoticed, but over time, as the cyst grows, symptoms gradually appear. Pleural involvement, whether primary or secondary, is rarely seen in clinical practice [12]. Clinical manifestations are variable and depend on the size, location, and pressure of the cyst on the surrounding lung tissue [8]. The most common symptoms are cough, dyspnea, fever, and chest pain [8, 12, 13]. In some rare cases, HC perforation can clinically manifest as anaphylactic shock. The most common complications are pleural effusion, empyema, and pneumothorax [2]. In most cases of pleural effusion or pneumothorax, significant mediastinal compression and displacement are observed, while empyema, one of the most serious complications, is associated with bacterial infection of a perforated cyst [12]. The diagnosis of pleural hydatidosis is not always easy. Differential diagnosis includes benign tumors, inflammatory masses, pathological conditions with formation of aero-liquid levels in the lungs, inflammatory processes, metastatic diseases, and malignancies. A standard chest radiograph is usually used as the first diagnostic method [6]. The most valuable diagnostic method for the detection of pleural HCs is a chest CT scan. CT findings can range from typical images of intact cysts that appear as round, homogeneous, and dense, through simple pleural effusions, to complicated empyema, pneumothorax, or hydropneumothorax [6, 10]. Sometimes it is possible to see calcifications of the cyst wall referred to as “eggshell calcifications” [5]. A chest CT scan also plays an important role in surgery planning. Lung ultrasound is rarely used for diagnosing pleural HCs; however, it can sometimes provide valuable information, particularly in the presence of complex cystic lesions, and it is safe to use in pregnant women [13]. In addition to radiological methods, various serological tests (i.e., ELISA, latex agglutination, and indirect hemagglutination test), as well as pathological examinations, are used for diagnosing hydatidosis [10]. These tests can be used in postoperative monitoring of patients, and also for screening. Some tests (skin tests, complement fixation, eosinophil count) have a tendency towards false positive results, so one should be careful when interpreting the results. Recent research

suggests that interleukin-4 could be useful for the identification of active cysts [14]. Fine-needle aspiration of HCs is not recommended for the diagnosis of pleural hydatidosis due to the high risk of complications such as pneumothorax, cyst rupture, and anaphylaxis [2]. Definitive diagnosis is made by thoracotomy and direct visualization of the cysts [12]. Surgical removal of intact HCs is the treatment of choice. However, it is necessary to completely remove the cysts without opening them; otherwise, it could lead to intraoperative dissemination of the parasites [15]. Intraoperative administration of 1% formaldehyde or hypertonic saline can prevent that by deactivating the cysts [9]. Pericystectomy is a common procedure, but other procedures like simple drainage, capitonnage, marsupialization, or resection of the lung can also be used, depending on the location and condition of the cyst [15]. According to Yalçinkaya et al. [9], cystotomy and capitonnage of the residual cavity are the methods of choice. Aribas et al. [6] state that cystotomy with capitonnage or cystectomy with capitonnage are the most preferred types of operations. However, some authors believe that capitonnage is not necessary after cystectomy and that only bronchial openings should be sutured and the cavity left open, arguing that capitonnage causes lung parenchyma deformation, prolongs surgery time, and increases morbidity [2]. In most cases, decortication is also performed. Radical lung resections should only be performed when the lung parenchyma around the cyst is destroyed and/or the lungs cannot expand [6]. Recurrence rates of 2–12% have been reported in the literature, while the operative mortality rate is 0.5–4% [9, 12]. Most authors suggest pharmacological treatment after surgery [2, 6]. During the administration of these drugs, regular monitoring of laboratory findings is required. Some authors suggest that percutaneous therapy of pulmonary hydatid disease is an effective alternative to surgical treatment in patients who have failed medical therapy [16, 17].

Conclusion

Hydatid cysts most commonly affect the liver and the lungs, while other locations are rarely involved. Pleural hydatidosis, although rare, most often occurs as a complication of rupture of pulmonary hydatid cysts. The diagnosis is based on radiological findings and serological tests, but intraoperative detection of the cyst is crucial. The treatment modality with the greatest therapeutic potential is surgical removal of the cysts. In countries where hydatid disease is endemic, prevention is of utmost importance. Our case highlights the importance of detailed radiological and intraoperative evaluation in distinguishing between the forms of pleural echinococcosis. Timely surgical intervention, supplemented by an adequate dose of albendazole, ensures a complete cure and prevents serious complications such as empyema or anaphylactic shock.

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The title should be placed above the table, and explanations (the legend) below it. Tables should be numbered with Arabic numerals in the order in which they appear in the text. Tables must be created exclusively in the Microsoft Word program using the menu Table–Insert–Table, with the exact number of rows and columns defined. Use Times New Roman font, 12-point size, single spacing. Tables must be clear and include all elements necessary for the proper interpretation of the data presented. If the displayed values have ranges or reference values, these must be specified.

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ABBREVIATIONS

Abbreviations should be used only when necessary, primarily for very long names of chemical compounds or for terms that are already widely recognized in abbreviated form (e.g., DNA). For each abbreviation—except standard units of measurement—the full term must be given at its first occurrence in the text (including the abstract). The use of abbreviations should be avoided in the title and abstract; in the title, abbreviations should be used only if absolutely necessary. For terms mentioned more than 3 times in the text, introducing appropriate abbreviations is recommended.

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In manuscripts written in English, decimal numbers should be written with a decimal point (e.g., 22.7), whereas in manuscripts written in Serbian, a comma should be used (e.g., 22,7). Whenever possible, numbers should be rounded to one decimal place and reported consistently throughout the manuscript (e.g., if one value is 32.2, all others should also be rounded to one decimal place, e.g., 32.0).

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ACKNOWLEDGEMENTS

The contributions of individuals who should be acknowledged but do not meet the criteria for authorship should be stated. Financial support (sponsorships, grants, equipment, etc.) should be disclosed, as well as the name of the project within which the research was conducted.

STATISTICAL ANALYSIS

In the Methods section, the applied statistical methods should be described in sufficient detail to allow verification of their correct use and reproduction of the analysis. Results must be presented numerically and clearly, with appropriate measures of variability and reliability (e.g., standard deviation, standard error, confidence interval). The type of study should be specified, and the manner in which it was conducted should be described. Inclusion and exclusion criteria must be stated. The software and the version of the computer program used for statistical data analysis should be reported. In the Results section, as well as in the legends of tables and/or figures, the statistical method used to analyze the presented results must be indicated. The p values should always be written with a leading zero (e.g., $p > 0.05$, not $p > .05$).

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References should be numbered with Arabic numerals according to the order of their first appearance in the text (including tables and figure legends). It is recommended that the majority of cited references be published within the last ten years. At least 80% of the cited references should be original research articles, while books, book chapters, and review articles should account for no more than 20% of the total number of references. All references, regardless of the language of the original source, must be cited in English, with the original language indicated in parentheses after the reference.

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Volume with a Supplement

Smith JA, Brown LM. Effects of vitamin D on immune response. J Nutr Sci 2024; 15(Suppl 2): S45–53.

Issue with a Supplement

Zhou Q, Shi R, Kopjar B, Wang H, Chen D, Li H, et al. Adjacent Intervertebral Disc Changes in Patients with Isobar Semirigid Dynamic Stabilization System. Global Spine J 2017; 4(1 Suppl): s-0034-1376699.

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Ozben T, Nacitarhan S, Tuncer N. Plasma and urine sialic acid in non-insulin dependent diabetes mellitus. Ann Clin Biochem 1995; 32(Pt 3): 303–6.

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Poole GH, Mills SM. One hundred consecutive cases of flap lacerations of the leg in ageing patients. N Z Med J 1994; 107(986 Pt 1): 377–8.

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Turan I, Wredmark T, Fellander-Tsai L. Arthroscopic ankle arthrodesis in rheumatoid arthritis. Clin Orthop 1995; (320): 110–4.

No Volume or Issue

Browell DA, Lennard TW. Immunologic status of the cancer patient and the effects of blood transfusion on antitumor responses. Curr Opin Gen Surg 1993: 325–33.

Pagination with Roman numerals

Fisher GA, Sikic BI. Drug resistance in clinical oncology and hematology. Introduction. Hematol Oncol Clin North Am 1995; 9(2): xi–xii.

Book

Printed Book

Ritter JM, Flower RJ, Henderson G, Loke YK, MacEwan D, Robinson E, et al. Rang & Dale's Pharmacology. 10th ed. London: Elsevier; 2023. p. 3630.

Book in electronic format

Shreeve DF. Reactive attachment disorder: a case-based approach [Internet]. New York: Springer; 2012 [cited 2012 Nov 2]. 85 p. Available from: http://dx.doi.org/10.1007/978-1-4614-1647-0

Chapter

In an edited book

Metcalf CS, Smith MD, Wilcox KS. Pharmacotherapy of the Epilepsies. In*: Brunton LL, Knollmann BC,* editors. Goodman & Gilman's The pharmacological basis of therapeutics. 14th ed. NY: McGrawHill; 2023. p. 385–411.

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Halpen-Felsher BL, Morrell HE. Preventing and reducing tobacco use. In: *Berlan ED, Bravender T,* editors. Adolescent medicine today: a guide to caring for the adolescent patient [Internet]. Singapore: World Scientific Publishing Co.; 2012 [cited 2012 Nov 3]. Chapter 18. Available from: http://www.worldscientific.com/doi/pdf/10.1142/9789814324496_0018

Website

Homepage

Diabetes Australia. Diabetes globally [Internet]. Canberra ACT: Diabetes Australia; 2012 [updated 2012 June 15; cited 2012 Nov 2]. 85 p. Available from: http://www.diabetesaustralia.com.au/en/Understanding-Diabetes/Diabetes-Globally/

Part of a website

Australian Medical Association [Internet]. Barton ACT: AMA; c1995-2012. Junior doctors and medical students call for urgent solution to medical training crisis; 2012 Oct 22 [cited 2012 Nov 2]; [about 3 screens]. Available from: https://ama.com.au/media/junior-doctors-and-medical-students-call-urgent-solution-medical-training-crisis

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Kimura J, Shibasaki H, editors. Recent advances in clinical neurophysiology. Proceedings of the 10th International Congress of EMG and Clinical Neurophysiology; 1995 Oct 15–19; Kyoto, Japan. Amsterdam: Elsevier; 1996.

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Bengtsson S, Solheim BG. Enforcement of data protection, privacy and security in medical informatics. In: *Lun KC, Degoulet P, Piemme TE, Rienhoff O,* editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sep 6–10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. p. 1561–5.

Dissertation

Knežević D. The importance of decontamination as an element of complex therapy of poisoning with organophosphorous compounds [Ph.D. Thesis]. Belgrade: School of Veterinary Medicine; 1988. (Serbian)

Other published articles

News article

Vujadinović J. The inconsistency between federal and republican regulation about pharmacies. In between double standards. Borba 2002 February 28; p. 5. (Serbian)

Holy Bible

Serbian Bible. Belgrade: British and Foreign Biblical Society; 1981. Book of Isaiah 2: 19–22. (Serbian)

Dictionaries and similar references

Kostić AĐ. Multilingual Medical Dictionary. 4th Ed. Belgrade: Nolit; 1976. Erythrophobia; p. 173–4.

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Рукопис рада и сви прилози уз рад достављају се **као један документ** (прилози су инкорпорирани у текст и позиционирани на крају рукописа иза одељка Литература) искључиво електронски преко система за пријављивање *Aseestant*. Ради очувања квалитета фотографија, препоручује се достављање слика и као посебних фајлова, јер Word може смањити њихову резолуцију, како би се избегла компресија слика и евентуални губитак квалитета.

Сви аутори и рецензенти морају бити регистровани корисници система са јединственом е-маил адресом. Регистрацију је могуће извршити на: http://aseestant.ceon.rs/index.php/vsp/user. Техничко упутство за коришћење система електронске пријаве доступно је на: https://aseestant.ceon.rs/index.php/vsp/about/submissions.

Уколико имате проблем са подношењем рукописа путем платформе *Aseestant* можете се обратити за помоћ Редакцији часописа слањем е-мејла на адресу: vsp@vma.mod.gov.rs.

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За писање рукописа користити програм *Word*, фонт *Times New Roman*, величину слова 12, проред 1,5. Величину странице подесити на формат А4, са левом маргином од 4 цм а преостале три 2 цм. Текст куцати без дељења речи (хифенације), а после сваког знака интерпункције ставити само један празан карактер. Ако се у тексту користе специјални знаци (симболи), користити фонт *Symbol*.

Подаци о коришћеној литератури у тексту означавају се арапским бројевима у суперскрипту, редоследом којим се појављују у тексту.

Странице нумерисати редом у доњем десном углу, почев од прве стране (изузимајући насловну страну).

При писању текста на енглеском језику придржавати се језичког стандарда *American English*. Обавезно је коришћење међународног система мера (SI). Изузетак чине крвни притисак (mm Hg) i temperatura (°C).

Приликом писања користе се стандардне скраћенице. Избегавати скраћенице у наслову и апстракту осим уколико је неопходно. Пун назив са скраћеницом у загради наводи се у њеном првом помињању, а даље у тексту само скраћенице, како у апстракту тако и у главном тексту. У закључку рада (не апстракта) нема скраћеница.

Не користити комерцијална имена лекова и других препарата, а уколико је то неопходно уз њихове називе обавезно навести и генеричка имена. Уређаји (апарати) се означавају фабричким називима, а податке о произвођачу (назив и место) навести у облим заградама. Уколико се у тексту користе ознаке које су спој слова и бројева, прецизно написати број који се јавља у суперскрипту или субскрипту.

Избегавати фонтове *bold* и курзив (*italic*) јер су резервисани за поднаслове. Изузеци су обавезно писање курзивом оних назива који се тако морају писати (нпр. гени или стране речи - латински).

Групе испитаника морају бити јасно дефинисане и доследно именоване кроз цео рад. За исти појам користити један, јединствен термин кроз цео рад. У одељку Резултати избегавати реченице које почињу са: „Табела X показује “ или „Слика X приказује“. Реченица треба да опише резултат, а ознака табеле или слике да стоји у загради на крају описа. Реченице не би требало почињати скраћеницом, бројем или датумом. Избегавати предугачке реченице које умањују јасноћу текста и дати предност краћим јасним реченицама. Закључак формулисати новим реченицама, без преписивања већ изречених. Превод радова на енглески језик посредством *Google Translate* може изазвати неразумевање текста и стога се не препоручује.

У избору кључних речи користити *Medical Subject Headings – MeSH* (https://www.nlm.nih.gov/mesh/meshhome.html). Кључне речи у прихваћеном рукопису не подлежу ауторској коректури, пошто су оне дескриптори из Тезауруса које одређују стручни индексери.

ОБАВЕЗНА ПРАТЕЋА ДОКУМЕНТА

ИЗЈАВА АУТОРА И АУТОРСТВО

За сваки рукопис који се подноси на разматрање за објављивање у ВСП неопходно је да аутор(и) достави(е) Образац за изјаву о ауторству (Изјаву аутора) да рад претходно није публикован и да није истовремено поднет за објављивање у неком другом часопису, да су рукопис прочитали и одобрили сви аутори који испуњавају критеријуме ауторства, и контакт податке свих аутора у раду (имејл адресу, број мобилног телефона). У овом обрасцу се аутори изјашњавају о сваком могућем сукобу интереса или његовом одсуству. Сви аутори морају Изјаву аутора потписати својеручно.

За додатне информације о различитим врстама сукоба интереса видети препоруке Светског удружења уредника медицинских часописа (*World Association of Medical Editors – WAME;* http://www.wame.org*)*.

ВСП поштује препоруке критеријума за ауторство које даје ICMJE (https://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html). Ауторство се заснива на испуњењу сва четири критеријума: значајном доприносу концепцији рада, добијању резултата или анализи/тумачењу резултата; критичкој ревизији рукописа од знатног интелектуалног значаја; одобрењу финалне верзије рукописа која ће бити објављена и преузимању одговорности за све аспекте објављеног садржаја. Сви други учесници који су допринели изради рада, али нису испунили прописане критеријуме требало би да буду наведени у Захвалници уз прецизирање доприноса раду. Потребно је да особе наведене у Захвалници дају писмену сагласност.

ЕТИЧКА САГЛАСНОСТ

Сва истраживања која укључују људе и/или хумани материјал морају бити спроведена у складу са препорукама ICMJE (https://www.icmje.org/recommendations/browse/roles-and-responsibilities/protection-of-research-participants.html) и Хелсиншком декларацијом, ревизија 2024 (https://www.wma.net/policies-post/wma-declaration-of-helsinki/). Скенирану страну дозволе Етичке комисије (ЕК) надлежне институције које је одобрила истраживање, на којој се види датум издавања и предмет истраживања, аутори су у обавези да доставе истовремено са рукописом. Дозвола ЕК се доставља на језику на коме је издата и енглеском језику (може и оверена копија).

У одељку Методе мора бити наведено да је студија одобрена од стране надлежног ЕК, уз навођење назива институције и броја одлуке, као и да је спроведена у складу са етичким принципима за истраживања која укључују људе и/или хумани материјал.

Анонимност пацијената мора бити заштићена у складу са ICMJE препорукама. За сва истраживања која укључују податке о пацијентима који омогућавају директну или индиректну идентификацију, аутори су обавезни да прибаве писани пристанак информисаног пацијента, да у рукопису назначе да је пристанак пацијента прибављен, и да га по потреби доставе Уредништву.

У случају истраживања на животињама, аутори су дужни да доставе одобрење надлежног ЕК који води бригу о поштовању међународних стандарда о употреби лабораторијских животиња у истраживачке сврхе.

Уредништво може одбити радове за које процени да нису изведени у складу са међународним етичким стандардима.

РЕПРОДУКОВАЊЕ ПРЕТХОДНО ОБЈАВЉЕНОГ ЗАШТИЋЕНОГ МАТЕРИЈАЛА И/ИЛИ НЕОБЈАВЉЕНОГ ТУЂЕГ МАТЕРИЈАЛА

Уколико се користе претходно објављене илустрације (фотографије, схеме) уз обавезно цитирање извора преузимања потребно је доставити дозволу (писано одобрење часописа у коме су објављене) за њихову објаву у ВСП. Уколико се користе туђе необјављене илустрације (фотографије, схеме) потребно је доставити дозволу аутора илустрација, за њихову објаву у ВСП.

ПЛАГИЈАРИЗАМ

Од 2012. године сви рукописи достављени на разматрање у ВСП подвргавају се провери на потенцијални (ауто)плагијаризам посредством *SCIndeks Assistant – Cross Check* (*iThenticate*). Рукописи код којих се докаже (ауто)плагијаризам биће одбијени. У зависности од степена и врсте утврђеног (ауто)плагијаризама ауторима се може изрећи забрана објављивања у ВСП-у (различите дужине трајања), уз обавештење надлежних тела у институцијама у којима аутори раде и релевантних професионаних удружења.

КОРИШЋЕЊЕ AI

Генеративна вештачка интелигенција (*artificial intelligence*-AI) или технологије које користе помоћ AI (AI-потпомогнуте) могу се користити само уз поштовање начела транспарентности (употреба AI мора бити јасно наведена у рукопису), одговорности (аутори остају у потпуности одговорни за тачност и оригиналност садржаја), проверљивости (сви учесници у публицистичком процесу морају проверити да AI није унела измишљене податке, цитате или тврдње) и поверљивости (ауторима и рецензентима је забрањено учитавање рукописа поднетих у ВСП у јавне AI сервисе).

Употреба AI алата је допуштена само за ограничене језичке и техничке интервенције у тексту рукописа: исправку граматике и правописа, стилско дотеривање ауторског текста, помоћ при форматирању, техничку асистенцију (попут исправљања кода). Аутори могу користити AI алате искључиво за креирање AI-потпомогнутог, али не и AI -генерисаног садржаја.

Аутори који су користили AI-потпомогнут садржај у обавези су да потпуно и тачно наведу употребу AI алата (тачан назив AI алата, датум приступа, коришћене упите и сврху употребе), гарантују оригиналност научног доприноса, избегавају било какву фабрикацију или манипулацију и поштују правила научне етике. Информације о коришћењу AI се наводе у одељку Методе или Захвалница.

Забрањено је користити AI алате за генерисање већег дела садржаја рукописа, креирање научних идеја, података и резултата, анализу и интерпретацију резултата, формирање закључака, измену слика, табела или графикона (укључујући графичке сажетке), измену података или референци.

Недвосмислено утврђена недопуштена употреба AI за последицу има одбијање рада.

AI ни у ком случају не може бити аутор или коаутор рада, нити може као аутор бити цитиран у одељку Литература.

Ради заштите поверљивости, ниједан део необјављеног истраживања достављеног ВСП не сме бити унет у велики језички модел од стране аутора или рецензента.

Аутори који су користили неки од AI алата су у обавези да приликом подношења рукописа поднесу и Изјаву о коришћењу AI.

ТИПОВИ РУКОПИСА

У ВСП се објављују следеће категорије и типови рукописа и саопштења: уводник, оригинални рад, претходно саопштење, кратко саопштење, приказ случаја и серија случајева, општи (наративни) преглед литературе, мини преглед, систематски преглед литературе, мета-анализа, систематски преглед литературе са мета-анализом, актуелна тема, у фокусу, рад из историје медицине/стоматологије/фармације, писмо уреднику, истраживачко писмо, клиничко истраживање, извештај са конгреса и научног скупа, приказ књиге, *In memoriam* и други прилози.

ОРИГИНАЛНИ ЧЛАНАК

Приказује нова и значајна открића у одређеној области уз детаљан опис коришћених метода истраживања, добијених резултата и изведених закључака. Листа референци треба да укључи најновије и најважније референце из области рада.

ПРЕТХОДНО САОПШТЕЊЕ

Представља приказ истраживања која нису завршена, са налазима који захтевају додатна истраживања и валидацију пре коначних закључака, али су добијене информације од интереса за научну и стручну јавност. Садржи сва поглавља као оригинални научни чланак, али у знатно скраћеном обиму. Аутори се подстичу да касније објаве пуну оригиналну научну студију са комплетним, валидираним подацима и свеобухватном анализом.

КРАТКО САОПШТЕЊЕ

Представља завршено истраживање које је мало по обиму, уско фокусирано са јасним закључцима на основу представљених резултата. Садржи сва поглавља као оригинални научни чланак, али у знатно скраћеном обиму. Сматра се коначном публикацијом тог специфичног, малог истраживања. Не може се поново објавити као чланак пуног обима (иако се подстиче накнадно истраживање које се надовезује на њега).

ПРЕГЛЕДНИ ЧЛАНЦИ

ОПШТИ (НАРАТИВНИ) ПРЕГЛЕД ЛИТЕРАТУРЕ

Преглед, критичка анализа и синтеза постојећих научних сазнања о изабраној теми. Аутори обухватају сву доступну припадајућу литературу за одређени временски период, приказују резултате релевантних истраживања, идентификују недостатке, ограничења или контроверзе и указују на правце будућих истраживања, дајући своје виђење проблема у виду закључног става. Аутори чланка ове категорије могу бити они који су објавили минимално пет радова публикованих у часописима с рецензијом (M20) из области прегледног рада.

МИНИ ПРЕГЛЕДНИ ЧЛАНАК

Сажет преглед постојеће литературе и најновијих достигнућа унутар дефинисаних аспеката одређене истраживачке области и њени нови и/или актуелни правци развоја.

СИСТЕМАТСКИ ПРЕГЛЕД ЛИТЕРАТУРЕ

Синтеза претходно објављених истраживања о одређеној теми коришћењем јасно дефинисаних и унапред одређених методолошких поступака за селекцију и евалуацију. Аутор мора да користи релевантне базе података, постави критеријуме укључивања и искључивања студија и примени транспарентну методологију.

МЕТА-АНАЛИЗА

Користи статистичке методе за комбиновање квантитативних података из више примарних студија како би се идентификовали општи трендови и проценила снага доказа о одређеној теми. Аутор мора да користи релевантне базе података, дефинише критеријуме за укључивање и искључивање и примени транспарентну и репродуцибилну методологију. Неопходно је јасно дефинисање истраживачког питања (PICOS оквир), навођење смерница за одабир и дијаграма тока за селекцију студија (PRISMA).

СИСТЕМАТСКИ ПРЕГЛЕД ЛИТЕРАТУРЕ СА МЕТА-АНАЛИЗОМ

Комбинује квалитативну и квантитативну синтезу, користећи статистичке технике за сумирање квантитативних резултата а квалитативну синтезу за описне/наративне налазе. Аутор мора користити релевантне базе података, јасно дефинисати критеријуме за укључивање и искључивање студија, и применити транспарентну и репродуцибилну методологију. Истраживачко питање мора бити јасно дефинисано према PICOS оквиру, уз навођење коришћених смерница за извештавање (нпр. PRISMA) и укључивање PRISMA дијаграма тока за приказ селекције студија.

АКТУЕЛНА ТЕМА

Разматра савремено, нерешено или контрадикторно питање од теоријског и практичног значаја, уз изношење сопствених резултата истраживања или најновијих важних података из литературе. Конструкција чланка је слободна а пожељне су кратке закључне напомене са јасном поруком.

У ФОКУСУ

Тематска, фокусирана анализа и/или кратак осврт на научни проблем који је у тематској области часописа, а који обрађује питање од значаја за научну заједницу и ширу стручну јавност.

КАЗУИСТИКА

ПРИКАЗ СЛУЧАЈА и СЕРИЈА СЛУЧАЈЕВА (≥4, ≤9)

Приказ случајева са ретком и необичном дијагнозом, дијагностичким процесом, стратегијама лечења, клиничким током, или исходом лечења, који могу бити од користи за клиничку праксу и медицинско образовање. Приликом писања потребно је користити CARE смернице (https://www.care-statement.org/writing-a-case-report). Неопходан је пристанак информисаног пацијента.

УВОДНИК

Уводници су нерецензирани текстови главног и одговорног уредника и/или чланова Уредништва намењени најави новог волумена, тематског броја, садржаја који су од значаја за струку и/или институције чијим члановима је часопис намењен као и уреднички текстови по позиву. Уводници не треба да садрже необјављене или оригиналне податке, а морају укључити изјаву о сукобу интереса.

ПИСМО УРЕДНИКУ

Нерецензирани коментар/критика текста објављеног у ВСП. Пишу се у слободној форми, уз евентуално навођење података из литературе. Не смеју садржати необјављене резултате. Објављују се према одлуци главног и одговорног уредника.

ИСТРАЖИВАЧКО ПИСМО

Кратки приказ оригиналног истраживања, који садржи увод, методе, резултате и дискусију у сажетом облику (без поделе у посебне целине са поднасловима) и максимално до 2 прилога (табеле/слике). Не садржи апстракт и кључне речи али мора да испуни све опште услове за разматрање рукописа (укључујући процес рецензије).

ИСТОРИЈА МЕДИЦИНЕ/СТОМАТОЛОГИЈЕ/ФАРМАЦИЈЕ

Материјал значајан за расветљавање појединих догађаја и/или приказ значајних личности из историје медицине/стоматологије/фармације, а посебно војне медицине/стоматологије/фармације.

КЛИНИЧКО ИСТРАЖИВАЊЕ

Оригинална рандомизована контролисана испитивања и опсервационе студије утицаја једног или више средстава или мера на исход здравља људи, клиничку праксу и здравствену политику. Рукописи морају бити припремљени у складу са међународним смерницама (нпр. CONSORT – https://www.consort-spirit.org/ или STROBE – https://www.strobe-statement.org/) и регистрована у неком од међународно признатих јавних регистара (нпр. ClinicalTrials.gov).

ПРИКАЗ КЊИГЕ

Садржи библиографске податке о публикацији (аутори, изворни наслов, издавач, место и година издања), њен кратак садржај и критичке коментаре садржаја, стила и значаја књиге у датој области. Рукопис не сме бити дужи од 2 странице.

ИЗВЕШТАЈ СА НАУЧНОГ ИЛИ СТРУЧНОГ СКУПА

Приказ активности научног или стручног скупа, уз истицање најважнијих реферата или закључака, односно препорука од значаја за шири круг читалаца ВСП.

ОБИМ РУКОПИСА

Целокупни рукопис рада чине: насловна страна, апстракти на српском и енглеском језику са кључним речима, главни текст рада, захвалност (по потреби), списак литературе, прилози (табеле, слике, графикони, схеме, цртежи).

Обим рукописа за категорије оригинални рад, општи (наративни) преглед литературе, систематски преглед литературе, мета-анализа, систематски преглед литературе са мета-анализом износи до 5 000 речи.

Обим рукописа за категорије мини преглед, претходно саопштење, кратко саопштење, приказ случаја, серија случајева, актуелна тема, клиничко истраживање, историја медицине/стоматологије/фармације износи до 3 000 речи.

Рукописи за остале категорије/рубрике могу имати највише 1 500 речи.

ПРИПРЕМА РАДА

НАСЛОВНА СТРАНА

На првој страници рукописа треба навести следеће:

1. Наслов рада без скраћеница;
2. Пуна имена и презимена аутора (без титула, уз навођење ORCID броја за све ауторе који га имају) са ознакама следећим редом ***, †, ‡, §, ‖, ¶, **, †† …** итд.
3. Пун званичан назив установа у којима аутори раде, место и државу у којој се установе налазе (знаци *, †, ‡, §, ‖, ¶, **, †† … итд.показују редом установе у којима аутори раде);
4. На дну странице навести име и презиме, адресу за контакт, е-маил адресу и број телефона (мобилног/*Viber* или *WhatsApp*) аутора задуженог за кореспонденцију.

АПСТРАКТ

На другој страни рада пишу се апстракт и кључне речи. Апстракт се пише кратким и јасним реченицама. За категорије оригинални рад, претходно саопштење, кратко саопштење, систематски преглед литературе са метаанализом, мета-анализа, клиничко истраживање, апстракт је структурисан и треба да има следеће делове: Увод/Циљ, Методе, Резултати, Закључак. Сваки од наведених сегмената писати као посебан пасус који почиње болдованом речи. Навести најважније резултате (нумеричке вредности) и ниво статистичке значајности. Закључак мора бити директно повезан са резултатима рада. Обим апстракта не сме да пређе 300 речи.

За категорије приказ случаја и серија случајева апстракт има следећу структуру: Увод (у последњој реченици навести циљ), Приказ болесника, Закључак. Сваки од наведених сегмената писати као посебан пасус који почиње болдованом речи. Обим апстракта не сме да пређе 250 речи.

За остале категорије радова, општи (наративни) преглед литературе, мини преглед, систематски преглед литературе, актуелна тема, у фокусу, историја медицине/стоматологије/фармације апстракт нема посебну структуру и не сме да пређе 200 речи.

Водити рачуна да српска и енглеска верзија апстракта буду међусобно тачни и прецизни преводи. Ниједна реченица не сме постојати у једној верзији а да није преведена у другој.

КЉУЧНЕ РЕЧИ

Испод апстракта навести пет до седам релевантних кључних речи или израза који указују на садржај рада. Препорука је да се не понављају речи из наслова рада. У избору кључних речи користити *Medical Subject Headings – MeSH* (https://www.nlm.nih.gov/mesh/meshhome.html).

СТРУКТУРА ГЛАВНОГ ТЕКСТА РАДА

Неопходно је да оригинални рад, претходно саопштење, кратко саопштење, мета-анализа, систематски преглед литературе са мета-анализом, клиничко истраживање садрже поглавља: Увод (кратак приказ предмета истраживања уз навод циља рада у последњем пасусу), Методе (прецизан опис одабира испитаника и примењених метода, укључујући статистичке методе, број дозволе сагласности надлежног ЕК), Резултати (приказани логичким редоследом без дуплирања приказа истих резултата на више начина), Дискусија (без понављања података који су већ наведени у одељку Резултати; дискутовати само добијене налазе довођењем у везу са другим релевантним студијама, повезати дискусију и закључке са циљевима рада, по потреби нагласити лимитације истраживања), Закључак (који проистиче из резултата датог истраживања), Захвалница (по потреби), Литература.

Рукописи из категорија општи (наративни) преглед литературе, мини преглед, систематски преглед литературе, актуелна тема, у фокусу садрже следеће целине: Увод (са одговарајућим поднасловима), Закључак, Литература.

Рукописи из категорије приказ случаја, серија случајева садрже следеће целине: Увод (циљ рада навести као последњи пасус Увода), Приказ болесника (идентитет болесника мора остати анониман), Дискусија, Литература.

Приказ болесника не сме имати више од пет аутора.

УПИТНИЦИ (Questionnaires)

Сви коришћени упитници који су употребљени као мерни инструменти за било који од испитиваних параметара, морају бити преведени на језик говорног подручја испитаника уз навођење доказа о извршеној валидацији и културолошкој адаптацији поднебљу испитаника.

ПРИЛОЗИ

Прилоге чији број треба да буде усклађен са дужином текста поставити на крај главног текста рукописа иза Литературе, а у самом тексту јасно назначити место које се односи на дати прилог. Крајња позиција прилога биће одређена у току припреме рада за публиковање.

Табеле

Наслов треба написати изнад табеле, а објашњења (легенду) испод ње. Табеле се означавају арапским бројевима према редоследу навођења у тексту. Табеле израдити искључиво у програму *Word*, кроз мени *Table–Insert–Table*, уз дефинисање тачног броја колона и редова који ће је чинити. Куцати фонтом *Times New Roman*, величином слова 12, с једноструким проредом. Табеле морају бити јасне и имати све елементе неопходне за правилно разумевање шта је у њима приказано. Уколико приказане вредности имају „опсег“ или „референтне вредности“, то се мора додати.

У легенди испод табеле треба објаснити све скраћенице наведене у табели и све ознаке (нпр. слова у суперскрипту или болдоване вредности). Такође, неопходно је прецизирати примењене статистичке методе.

Слике (илустрације)

Под сликама подразумевамо све облике графичких прилога (фотографије, цртежи, схеме и графикони). Слике треба уградити у рукопис на крају текста, после литературе и после табела (ако их има). Слике се означавају арапским бројевима према редоследу навођења у тексту. Велика слова А, Б, Ц итд. треба користити за означавање делова вишеделних слика. Слова, бројеви и симболи треба да су јасни и уједначени, а довољне величине да приликом умањивања буду читљиви. Додаци приказани на сликама морају бити сачувани као фотографије (не као измењиви графички елементи), тако да се њихов положај не може мењати, како би се обезбедила тачност података приказаних на слици. Примају се искључиво дигиталне фотографије са минималном резолуцијом од 300 *dpi* и формата JPEG, PNG или PDF. Слике које не задовољаавају наведене услове неће бити прихваћене за објаву. Димензије достављених слика би требало да буду приближне димензијама у којима ће слика бити објављена. Уколико аутори нису у могућности да доставе дигиталне фотографије, онда оригиналне слике треба скенирати у резолуцији 300 *dpi* и у оригиналној величини и као такве их доставити. Сви подаци на схемама и графиконима треба да буду исписани безсерифним фонтом ради лакше читљивости (нпр. *Arial*, *Helvetica*), величина слова не мања од 10 *pt*. Мерне јединице и скале морају бити јасно назначене. Децимални бројеви на графиконима морају бити приказани са тачком, а раздвајање хиљада мора бити означено зарезом (нпр. 1,234.56).

Видео-прилози (илустрације рада) могу трајати 1–3 минута и бити у формату *avi, mp4*(*flv*). Уз видео доставити посебно слику која би била илустрација видео-приказа у е-издању и објављена у штампаном издању, као и линк ка платформи где је видео већ постављен.

У легенди испод илустрација треба објаснити све скраћенице, симболе, бројеве или слова који се користе за објашњење појединих делова слике. У случају графикона прецизирати примењене статистичке методе (по потреби), а код фотомикрографије навести детаље о врсти коришћеног бојења и увећању.

Уколико се приказују фотографије особа (болесника), лик мора бити „замућен“ или је потребно обезбедити писану дозволу лица са фотографије за њено коришћење. На прилозима (снимци рендгена, скенера, ултразвука, итд.) потребно је уклонити све што може да идентификује болесника. Уколико је слика већ негде објављена потребно је цитирати извор уз писано одобрење ако се ради о заштићеном материјалу.

СКРАЋЕНИЦЕ

Скраћенице користити само када је неопходно, и то за веома дугачке називе хемијских једињења, односно називе који су као скраћенице већ препознатљиви (нпр. ДНК). За сваку скраћеницу, осим стандардне јединице мере, навести пун назив при првом навођењу у тексту (укључујући апстракт). У наслову и апстракту избегавати коришћење скраћеница, у наслову их користити само ако су неопходне. За појмове који се у тексту помињу више од три пута препоручује се увођење одговарајућих скраћеница.

ДЕЦИМАЛНИ БРОЈЕВИ

У тексту рада на енглеском језику децималне бројеве писати са тачком (нпр. 22.7), а у тексту на српском језику са зарезом (нпр. 22,7). Кад год је то могуће, број заокружити на једну децималу и писати доследно кроз цео рад (нпр. ако је једна вредност 32.2, све остале морају имати једну децималу, нпр. 32.0).

ЈЕДИНИЦЕ МЕРА

Дужину, висину, тежину и запремину изражавати у метричким јединицама (метар – m, килограм (грам) – kg (g), литар – L) или њиховим деловима. Температуру изражавати у степенима Целзијуса (°C), притисак крви у милиметрима живиног стуба (mm Hg). Резултате клиничких и биохемијских мерења наводити у метричком систему према Међународном систему јединица (SI).

ЗАХВАЛНИЦА

Изнети допринос особе којој треба одати признање, али која не испуњава критеријуме за ауторство. Навести финансијску помоћ (спонзорства, стипендије, опрема и друго), као и назив пројекта у оквиру кога је истраживање спроведено.

СТАТИСТИЧКА АНАЛИЗА

У одељку Методе детаљно описати примењене статистичке методе како би била омогућена провера исправности њихове примене и репродукција анализе. Резултати морају бити нумерички јасно приказани уз одговарајуће показатеље варијабилности и поузданости (нпр. стандардна девијација, стандардна грешка, интервал поверења). Прецизирати тип студије и описати начин на који је изведена. Навести критеријуме укључења и искључења. Навести софтвер и верзију компјутерског програма у коме је извршена статистичка обрада података. У одељку Резултати као и у легендама табела и/или прилога навести статистички метод који је коришћен за анализу приказаних резултата. Вредности *p* се увек пишу са почетном нулом (нпр. $p > 0.05$ а не $p > .05$).

ЛИТЕРАТУРА

Референце нумерисати редним арапским бројевима према редоследу навођења у тексту (укључујући табеле и легенде прилога). Препоручује се да већина цитираних радова буде млађа од десет година. Препоручује се да број цитираних оригиналних радова буде најмање 80% од укупног броја референци, односно број цитираних књига, поглавља у књигама и прегледних чланака мањи од 20%. Сви радови, без обзира на језик извора, цитирају се на енглеском језику, а изворни језик наводи се у загради, иза цитиране референце.

Сви подаци о цитираној литератури морају бити тачни, а цитирани радови лако приступачни читаоцима. Уз сваку референцу навести DOI број. Препоручује се цитирање само радова објављених у часописима које индексирају *Current Contents, Index Medicus* (*Medline*), *Excerpta Medica, Scopus, Web of Science*.

Није дозвољено цитирање апстраката, секундарних публикација, усмених саопштења, необјављених радова, службених и поверљивих докумената, Википедије, препринт објава и *in press* чланака, повучених радова (*retracted article*), радова објављених у предаторским часописима.

Приликом цитирања сајтова, не може се цитирати насловна страна већ се мора цитирати она страна са које је информација преузета. Свака наведена референца мора бити доступна за проверу *online*. Уколико референца не постоји на интернету (нпр. архивски материјал и сл.), аутор мора да достави извор одакле је преузео цитирану литературу односно може сликати или скенирати документ и послати на е-мејл: strliteratura@gmail.com.

Референце се цитирају према Ванкуверском стилу који је успоставио ICMJE (https://connect.ebsco.com/s/article/Citing-Articles-in-Vancouver-ICMJE-Style?language=en_US).

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